INTERNATIONAL RECORD OF MEDICINE

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ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

Symposium on the Management of Mental Retardation in Adolescents

Part I

Guest Editor—I. Newton Kugelmass, M.D., Ph.D., Sc.D.

Introduction — I. Newton Kugelmass

History of Training and Treatment of Retarded Adolescents — Isaac N. Wolfson

Clinical Evaluation of the Adolescent Retardate — Harriet E. Blodgett

The Metabolic Basis of Some Inborn Intellectual Disorders in Adolescents — I. Newton Kugelmass

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Study of an Experimental Syndrome of Excitation-Hypotonia — H. Laborit, J. M. Jouany, J. Gerard, and J. Drouet

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FELIX MARTI-IBAÑEZ, M.D., Editor-in-Chief
Professor and Chairman of the Department of the History of Medicine,
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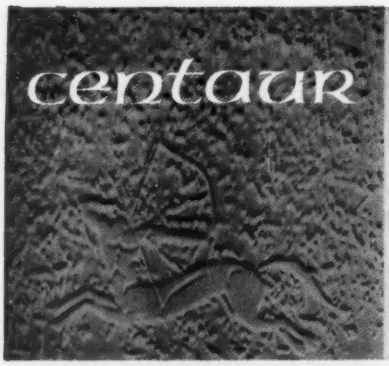

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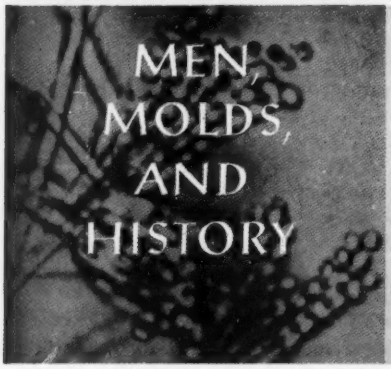

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INTERNATIONAL RECORD OF MEDICINE

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Symposium on the Management of Mental Retardation in Adolescents

PART I

GUEST EDITOR—I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D.

Introduction

I. Newton Kugelmass, M.D., Ph.D., Sc.D.

CONSULTANT TO THE DEPARTMENTS OF HEALTH AND HOSPITALS

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Our symposium on the medical management of adolescent retardates approaches ancient problems with new solutions. Aments are recognized first in early childhood, early school years, or early adolescence, depending on the severity of the retardation. It may originate in the child's internal environment or external environment or in the interaction of the two to produce defects of the central nervous system, always influenced by associated psychological and sociological factors. The diminished capacity for growth in perceptual and conceptual integration and consequently in environmental adjustment gradually emerges as deficient voluntary power in a defective adolescent personality.

We have delimited the field to adolescence because the peak incidence of mental retardation rises rapidly at the onset of pubescence and drops abruptly during late adolescence paralleling the rapid developmental tempo of this final growth cycle. It augments social sensitivity to intellectual disorders in the dwindling anticipation of the family objective that youth is the time to do something and become somebody. This goal is obliterated by mental retardation, a symptom of underlying disease rather than a clinical entity. Its recognition is possible only in relation to the persistent demands of cultural settings, which usually wane after the school years for the milder forms of amentia only to be replaced by a social rather than a biological diagnosis.

Mental deficiency is a rewarding field for systematic inquiry with its salient phe-

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Part II of this Symposium will appear in the April issue.

nomena less diverse and elusive than those of other branches of pediatrics. Yet the whole field was enveloped in nihilistic attitudes, derogatory stigmas, and pessimistic predictions until our revolutionary era revealed mental deficiency as a pathological process that can be studied and modified by the newer methods of clinical science. Rational therapeutic procedures were evolved not only for exogenous but for endogenous types of amentia leading to highly successful adjustments, even in the presence of relatively high degrees of intellectual defects, if the adolescent is emotionally healthy and highly motivated. Progressive therapeutic patterns involve early recognition, special classes, sheltered workshops, vocational habilitation, and medical supervision.

The distinguished participants in this clinical seminar clarify the bewildering panorama of scientific progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Dr. Wolfson discusses the history of ament training; Dr. Blodgett, the evaluation of adolescent retardates; Dr. Kugelmass, the metabolic basis of intellectual disorders; Dr. Green, the ego structure of the retarded personality; Dr. Doll, the American system of education for the retarded adolescent; Dr. Schoneli and Mr. McLeod, the British system; and Drs. Heald and Oberman, perspectives of adolescent aments. We close with Bailey's pronouncement: " 'Tis inspiration expounds experience."

SYMPOSIUM ON MEDICINE AND WRITING

The Symposium on Medicine and Writing that originally appeared in the INTERNATIONAL RECORD OF MEDICINE has been published recently as a Monograph. The articles included in this Monograph are: "The Editing of a Modern Medical Textbook" by Russell L. Cecil; "Plain Talk and Clear Writing" by Morris Fishbein; "The Principles of Bibliographic Citation" by John F. Fulton; "The Art of Communication" by Joseph Garland; "On Writing a History of Medicine" by Douglas Guthrie; and "Minerva and Aesculapius: The Physician as Writer" by Félix Martí-Ibáñez.

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History of Training and Treatment of Retarded Adolescents*

Isaac N. Wolfson, M.D.

DIRECTOR, LETCHWORTH VILLAGE
THIELLS, N. Y.

Not as a presentation of a new concept but rather as an introduction to the topic under discussion, it is deemed advisable to repeat the well-known fact that mental retardation is not a single entity. It is a symptom of varied conditions and of different etiologies and appears in different degrees. The degree of retardation is measured by psychometric tests and expressed in the so-called intelligence quotient rating. For some time it has been recognized by many workers in the field that this test has limited application in assaying a person's potentialities. In the 1920's, Dr. Fernald, who was then superintendent of the Walter E. Fernald State School in Massachusetts, already emphasized the study of the total personality rather than dependence on psychometric tests only, and he postulated 10 different fields of inquiry as essential to the study and diagnosis. At best the psychometric test measures only the intellectual capacities for school learning. Sarason called attention to the fact, recognized by many, that a marked discrepancy exists between performance on intelligence tests and the non-test problem—solving behavior of an individual in everyday life. The latter is often on a higher plane than is predicted by performance on psychometric tests in earlier years.

Although all the limitations of psychometric rating are recognized in the discussions of the subject, the degrees of retardation are still, by and large, expressed in terms of these ratings. Generally speaking three broad degrees of retardation are recognized, the severely retarded (intelligence quotient up to 19), moderately retarded (intelligence quotient 20 to 49), and mildly retarded (intelligence quotient 50 to 70). These correspond to the old obsolete terms of "idiot," "imbecile," and "moron." (There is a revised psychometric rating scale, which appears in the new *Manual on Terminology and Classification in Mental Retardation*, but for the purpose of this discussion the above-mentioned scale, which still is used by most people, will suffice.)

Statistically the first two groups represent about 20 per cent of all the mentally retarded, and it is generally agreed that most of these cases are of organic nature. The mildly retarded represent about 4 million or 80 per cent of the estimated number of the retarded in the United States.

There is a considerable controversy as to the etiology of this latter group. At the one extreme these cases are considered to be of genetic origin and thus are labeled

* This paper was written in collaboration with Stanley Powell Davies, Ph.D., whose two books *Social Control of the Mentally Deficient*, published in 1930, and *The Mentally Retarded in Society*, published in 1959, were used as the source material for historical background.

by some the "familial type," while at the other extreme they are considered to be mostly a result of environmental and cultural factors. These mildly retarded children are sometimes not recognized as such until school age, and in their adulthood they are absorbed into the general population and often are no longer identified as mentally retarded, unless for some reason or other they come to the attention of some social agency.

This paper will be mainly concerned with mildly retarded adolescents.

THE DEVELOPMENT OF EDUCATIONAL AND CUSTODIAL FACILITIES

Prior to the beginning of the nineteenth century no provisions were available for the care or training of the mentally retarded. Space does not permit going into detail as to the attitude toward the mentally retarded in the course of history. Suffice it to say that the status of the mentally retarded varied in accordance with dominant social attitudes and superstitions of each epoch.

The first attempt to train a mentally retarded boy occurred accidentally in the beginning of the nineteenth century. A group of hunters in France caught a wild boy in the woods of Aveyron and brought him to Paris. The prevalent opinion at the time was that the mentally retarded were incurable and not amenable to any training or teaching. Two famous physicians of that time, who both supported this belief, happened to disagree in the diagnosis of the boy's condition. Dr. Philippe Pinel, after observing the boy's condition, considered him an idiot (this was a generic term applied to all mentally retarded persons at the time), whereas Dr. J. M. G. Itard, the chief medical officer of the French National Institute for the Deaf and Dumb, disagreed with Pinel, his former teacher, and attributed the boy's apparent retardation to environmental factors. Therefore, Itard undertook to train him to determine what might be the degree of intelligence and the nature of ideas of a boy who had been deprived from birth of all education and had lived apart from other human beings.

The scientific literature in the field of mental retardation began with the publication in 1801 of Itard's work, *Education of a Savage Man*, in which he described the first months of work with the boy. Itard was encouraged by the first slight evidence of progress and continued his work with this boy for about four years longer. As time passed, however, Itard reluctantly came to the conclusion that his teacher, Pinel, had been right and that the "Savage of Aveyron" was actually an idiot. Itard felt that his five years of labor had resulted in failure. However, his work received the recognition of the French Academy of Medicine. Itard's pioneering efforts were the beginning of a scientific approach to mental retardation. To prove that the feeble-minded were capable of some degree of education was a momentous contribution.

Although Itard did not continue to work with the mentally retarded, he inspired his student, Edwin Séguin, to dedicate his life to the understanding and training of them. Séguin championed their cause as one of the most neglected groups of his day. He founded in Paris, in 1837, the first successful school for the specific

purpose of educating the retarded. The fame of Séguin traveled far and his school attracted visitors from many parts of the world. As a result, facilities for training the mentally retarded were organized in Europe and in the United States.

Dr. Samuel G. Howe, director of the Perkins Institute for the Blind in Boston, was the first person in this country to attempt to train a few mentally retarded persons in his institution. In 1848 Dr. Harvey B. Wilbur of Massachusetts, after becoming acquainted with the work of Séguin, established the first private school for the education of the mentally retarded.

In 1846 legislation was introduced in New York State and Massachusetts to provide public facilities for the education of the mentally retarded. As a result, experimental schools were established, which later became permanent institutions—Fernald State School, Waverly, Massachusetts, and Syracuse State School, Syracuse, New York. As time progressed, other states gradually built similar state schools. Early schools were started with a humanitarian attitude and a high wave of optimism in the belief that most mentally retarded persons could be trained to restore them to the community as self-supporting individuals. However, gradually the leaders in the field came to realize that mental retardation was not curable or even greatly improvable. It should be stated that only the more severely retarded were recognized at the time. As a result, a new problem arose. It soon became evident that the states had to provide facilities for indefinite institutional care for the growing number of mentally retarded, as only a very small proportion of the pupils could be returned to the community. So the idea of institutions for the mentally retarded as purely an educational problem had to be abandoned. The states had to provide facilities for prolonged or permanent care of the mentally retarded, and as a result institutions were gradually established in various states for that purpose. In the beginning, the custodial aspect was uppermost in the state institutions for the mentally retarded. Because the early hopes for curing the mentally retarded were not realized, the state authorities felt that their duty was done by providing kindly custodial care and that it was useless to spend time and effort to train the lower grade patient.

Thus the nineteenth century witnessed a promising beginning of organized scientific work in behalf of the mentally retarded, saw the development of a sound educational procedure, brought defeat of the hope of curing the mentally retarded, and marked the development of state institutions. The beginning of the twentieth century saw a general public awakening to the mentally retarded as presenting a social problem of the first magnitude.

PERIOD OF PESSIMISM AND ALARM

Séguin, Howe, and other pioneers had preached the gospel of sympathetic understanding toward the mental defective. They were pictured as weaker members of the human family who had to be protected from gross abuse at the hands of society. At the turn of the century, this picture was completely changed. For a period of two decades or more, both the man of science and the man on the street regarded the

feeble-minded as the most potent if not the sole source of all social evils. The mental defective, by general consent, was nominated to the position of primary social menace.

Several scientific developments at this time, which in themselves were of great value to scientific progress, indirectly contributed to the changed attitudes toward the mentally retarded. These were the development of the Binet-Simon Intelligence Tests, the development of the eugenic movement, and the revival of interest in the Mendelian laws of heredity, which initiated certain hereditary studies with exaggerated conclusions based to a great extent on hearsay evidence.

In 1905 Binet and Simon invented a test to measure mental age. On the basis of the examination of many children, specific tests were established for different ages. Those who tested below the established norm for their age were classified as mentally retarded. The norm for adolescents and adults was 12 years. Incidentally, some time later Dr. Terman modified the psychometric rating by introducing the intelligence quotient, which represents the ratio between the mental age as revealed by the psychometric tests and the actual chronological age of the subject tested.

Dr. Fernald, although recognizing the limitations of the test, considered Binet's theory and technique for measurements of variations of human intelligence as most significant in explaining mental retardation, facilitating its diagnosis, and furnishing accurate data for training and education of the mentally retarded. The test was introduced in the United States in 1908 by Dr. Henry H. Goddard, director of research laboratories at the Training School for the Feebleminded at Vineland, New Jersey. Mainly through his sponsorship, the intelligence test gained ready acceptance and was soon widely employed throughout the country in detecting and grading mental deficiency. Application of this test to various groups outside of institutions, such as school children, people confined to penal institutions and poorhouses, and finally the draftees of World War I, half of whom tested below 12 years of age, caused a serious concern over the alarming prevalence of mental retardation. The preponderance of mental deficiency among social misfits was discovered by the British Royal Commission when they studied the population of penal institutions. It was estimated that a substantial percentage of the population were intellectually subnormal. Besides being involved in the more serious offenses such as murder, rape, and arson, these persons filled the ranks of the beggars, vagrants, and petty thieves. These findings led to the inference that an organic connection existed between feeble-mindedness and crime, pauperism, and degeneracy. The refinements of the intelligence test were responsible for bringing to light a very large group of persons of borderline intelligence hitherto largely unrecognized as retarded.

While these revelations of the wide extent of mental deficiency in the community were being made, other studies were indicating that subnormal persons tend almost invariably to reproduce and multiply their kind in ever-growing numbers. Public attention was consequently directed toward the eugenic aspects of the problem. Stimulated by the fast-growing interest in eugenics, it was not long before research workers began to apply the Mendelian theory to the transmission of human characteristics and among them mental retardation.

The revived interest in the question of the transmissibility of mental defect that

sprang up in connection with the eugenics movement led to various studies of the family histories of certain supposedly defective stocks. These studies furnished a mass of data that was widely accepted as concrete evidence that mental deficiency is strongly and preponderantly hereditary.

One such study was *The Jukes* by Dr. Dugdale, which was first published in 1877 and reprinted in 1910. Many similar studies of the so-called "royal" lines of degeneracy were published at the time. The most important study, which reinforced the then-prevalent belief that mental retardation is hereditary, was that published by Dr. Goddard in 1912, the *Kallikak Family*. This book became the best known and most widely quoted of all the studies of defective stock. The Kallikak findings brought Dr. Goddard to the conclusion that "feeblemindedness is hereditary and transmitted as surely as any other character." Without exception, all these studies led to the same basic conclusion: mental defect was mostly hereditary; it was a principal, if not the most important, cause of many social ills.

Of the many remedies suggested to correct this most serious social problem, two were widely accepted—sterilization and segregation.

Eugenic sterilization was adopted by a number of states as a means of ridding the race of its defective germ plasm. It is still recognized in many states. The value of eugenic sterilization was a matter of divided opinion; in any event it has not proved to be very effective in reducing the incidence of mental retardation. The reasons for its failure were the fact that the origin of many kinds of mental deficiency is still unknown, the finding that the union of two mental defectives does not always result in a defective offspring, and the fact that 89 per cent of mentally retarded children spring from normal parents. Sterilization of institutional populations reaches only a very small number of the mentally retarded. The only area where sterilization may be of value is in individual cases for socioeconomic reasons.

While there was disagreement on the subject of sterilization, there was a general consensus of opinion in favor of segregation as the most practical and acceptable means of control of the mentally retarded. The prevalent alarm concerning feeblemindedness resulted in appointment in many states of special investigating commissions, which usually clamored for more beds in institutions. The general opinion was that "the data revealed that illegitimacy, attempted murder, theft, forgery, arson, prostitution, drunkenness, destitution and disease are salient features of the social cancers of these incompetents." In spite of tremendous pressure, institutional provisions for the mentally retarded never reached more than 8 per cent of the estimated number of mental defectives in the community.

During the so-called alarmist period, the administrators and personnel of institutions held the same opinion about the menace of mental retardation as did the public at large. Therefore, permanent or lengthy confinement was the order of the day.

This was the status of the mentally retarded in the early part of the twentieth century.

To sum up, prior to the nineteenth century, the mentally retarded were considered incapable of benefiting by training or teaching; therefore, no such facilities were provided for them.

The nineteenth century witnessed a promising beginning of organized scientific work in behalf of the mentally retarded, saw the development of a sound educational procedure, brought defeat of the hope of curing the mentally retarded, and marked the development of the state institution.

In the early 1900's, mental retardation presented a rather limited problem. A majority of the mentally retarded recognized at the time were of a severe type and represented a relatively small group. By 1915, the wide application of psychometric tests brought to light a large group of mildly retarded who formerly were not recognized as such. Alarmed by sheer numbers, alleged antisocial conduct by a majority of them, and assumed hereditary nature of the condition, society became quite concerned and the mentally retarded became a major social problem. As a result, two major measures to control the situation were introduced—sterilization and segregation.

CHANGE IN ATTITUDE

In about the third decade of the present century, after a more critical appraisal of the new scientific discoveries, the errors of the alarmist theories and conclusions became evident. As a result a more realistic attitude toward mental retardation was developing.

One of the important determining factors in the change of attitude was a follow-up study made by Dr. Fernauld, published in 1919, of patients discharged from the Waverly State School after a period of 25 years.

In spite of the fact that the study included patients who were discharged from the institution when life-long segregation was believed to be the best policy, that the majority of cases were discharged under protest against the advice of institutional authorities and quite a few were "runaways," the results obtained under these largely unfavorable circumstances were little short of a revelation. It was found that many of these people, contrary to anticipated findings, were making a satisfactory adjustment.

With this more enlightened point of view and a better understanding of the mentally retarded, the institutional attitude also changed. It was gradually accepted that not all of those confined to an institution had to remain there indefinitely. Many of them, after proper training and rehabilitation, could return to the community. As a result a program for the release of patients supported by legislative sanction was developed. With the enlightened attitude the institutions have been gradually transformed from custodial repositories to training centers. A modern institution for the mentally retarded today is equipped with a residential medical staff, an attending staff of physicians from the community in various specialties who provide the necessary medical and surgical care for the patients, departments of social service, psychology, education, occupational therapy, and recreation, full- or part-time chaplains of the three major faiths, a research department and an in-service training program for personnel. The program of a modern institution is geared to provide the best nursing and medical care to the severely retarded and physically handicapped; to make life happier, more tolerable and meaningful for the moder-

ately retarded, who, because of lack of community facilities for their care and supervision may remain institutionalized for an indefinite period; and to provide education, training, rehabilitation, and psychiatric treatment for the mildly retarded who should be considered as only temporary residents, and make every effort to have most of them return to the community to lead useful and satisfying lives within the limits of their capacity.

Whereas, formerly, discipline and order in the institutional setting were maintained by punitive and retaliatory measures, this attitude is slowly changing to maintenance of discipline by an understanding and sympathetic attitude with emphasis on creating a therapeutic milieu for the boys and girls.

DELINQUENCY

A small number of the institutionalized mildly retarded presented a more serious problem than could be handled in an open institution. They not only presented the problem of management of themselves but disrupted the adjustment of the other patients. Therefore, in a few states special facilities for these so-called "defective delinquents" have been established. The transfer of a few difficult patients from institutions for mentally retarded improved greatly the management of the institutional population. On the other hand, the more restrictive discipline and the special program directed specifically to this type of defective in the institutions for defective delinquents had a beneficial effect on them.

Statistical analyses of large groups of delinquents by several students of the problem revealed that only about 10 per cent of them were clearly mentally retarded, whereas the majority of them were found to be of normal intelligence. It was further found through follow-up work with the mentally handicapped delinquents that environment had largely determined their behavior, and it was asserted that the mentally subnormal properly cared for do not develop criminalistic tendencies. Several of the reports indicated that the mentally retarded are more prone to be "caught" because they are not as clever as normal offenders, who are more quick to slip through the fingers of the law.

In making a fair estimate of the percentage of mental defectives among delinquents, it has been pointed out also that the low score of an individual on a psychometric test in some cases may be due not to inherent mental deficiency, but to emotional and other factors resulting from the attitude of the offender toward his apprehension or imprisonment.

All these studies point out that there is apparently no inborn or universal or necessary connection between inferior intelligence and social offenses. The mildly retarded contribute more than their due proportion to minor social offenses, largely because they are more likely to be underprivileged, coming, in large part, from families lacking good parental guidance, decent housing, adequate economic resources, and a wholesome neighborhood environment.

EDUCATION

Of the estimated total number of mildly retarded only about 1 per cent or 40,000

are institutionalized. They, especially those who are admitted in their early adolescence, do not enter the institution primarily because of their mental retardation but rather because they present some behavior or personality disorder. Most of these disorders are environmentally conditioned and therefore a large percentage of these people eventually leave the institution. The writer commented in a follow-up study of a group of institutionalized patients 10 to 12 years after they left the institution and eight years after discharge from any supervision: "Apparently the sheltered, orderly life of an institution, the education and training program geared in tempo and scope to the capacity of the patients, and perhaps some emotional support received by an individual boy or girl from some person in authority have helped the inherently stable individuals to pass through the turbulent stage of adolescence, away from untoward environmental influences and frustrating excessive demands and reach a certain degree of maturity to be able to face the world again."[5]

Outside of the institutional facilities, very little provision is made for training or treatment of the mildly retarded in the community. For a long time school authorities kept the retarded in the regular classes, considering them slow learners, lazy, or indifferent, without recognizing the fact that they were lacking intellectual capacity for regular classwork, until modern psychology showed the true state of these children's limitations.

Once the public school authorities became aware that the mentally retarded were present in large numbers in their enrollment, the educators turned their attention to organization of special classes or special schools for these handicapped pupils.

The responsibility of the school for educating the subnormal child has been generally accepted and appreciable progress in formation of special classes is being made each year. The first school to establish a special class for retarded children was in Providence, Rhode Island, in 1896. Other cities soon followed. As time progressed many states enacted statutes making mandatory or permissive the establishment of special classes for mentally handicapped children in connection with public schools.

Unfortunately, the schools are still concerned with their mentally handicapped pupils only during school hours and fail to maintain a close and helpful contact with the child's other environment.

Although the major emphasis in the special classes for the retarded has been placed on vocational training in preparation of the students for employment after completing studies, so far these goals have been accomplished only to a limited degree. Research into the field indicates that a large number of mentally retarded who hold jobs have not been trained for them, did not receive professional counseling, and were not placed on the jobs by specified agencies. The majority of those employed have found their own jobs, hit or miss. A special study of selected groups of the employed mentally retarded points out that there is a tremendous difference between blundering into a job and receiving skilled help in training and placement.

PSYCHOTHERAPY

Up to a few years ago the status of psychotherapy of the mentally retarded was

the same as that of education of the mentally retarded before Itard. In this respect the mentally retarded were apparently considered subhuman and therefore not amenable to psychotherapy. Sarason stated in the introduction to *Counseling and Psychotherapy with the Mentally Retarded*[6]: "This book of writings on therapeutic approaches with the mentally retarded could not have been published ten years ago for a variety of reasons. First, there were very few professionals who were interested in the area. Second, the relevant writings, in terms of quantity and quality, would not have justified a book. Third, very few people would have been interested in reading, let alone buying, such a book."

Psychiatric services in the community for the emotionally disturbed retarded or those with deviant behavior are still very meager. The child guidance clinics reject these adolescents when psychometric tests reveal their mental retardation.

Those of us with psychiatric background who have close contact with mildly-retarded adolescents in institutions recognize the fact that these people have the same psychological problems and the same reactions to conflicts and they respond to a sympathetic and understanding attitude in the same way as the so-called normal adolescent. As a matter of fact, if one makes an effort to communicate with them in language that they can understand, one soon forgets that he is dealing with mentally retarded persons. These boys and girls are capable of establishing good rapport and they sometimes surprise one by their judgment and their sense of values and responsibility.

Unfortunately, we still know very little about the personalities of mentally retarded persons because the staffing of professional personnel in institutions is so limited that there is very little opportunity to study individuals or small groups of patients intensively and there has been, so far, very little interest in psychodynamic studies of the noninstitutionalized mildly retarded. A great deal has been said by observers of the mentally retarded about their conduct, attitudes, and adjustment. Very few persons, however, concern themselves with the matter of self-evaluation of the mentally retarded and their inner feelings, aspirations, and frustrations.

We are becoming aware, however, of the fact that the emotional needs and problems of the mentally retarded are no different from those of normal persons. As a matter of fact, in addition to problems faced by normal adolescents they must face some problems that are the result of their mental retardation. Some of these problems may arise from their relationship with parents who either overtly reject the child or express their rejection in overindulgence or overprotection, and from their relationship with their siblings. As they get older these children become confronted with the problems of contact with their contemporaries in the community. The emotional problems faced by a retarded child in a school setting present additional difficulties in adjustment. The reactions of these children to their problems are no different than those of normal children. A mentally retarded child has the same basic needs of affection, security, and identification and he responds in the same manner to frustrations.

Kanner stated in his pamphlet *A Miniature Textbook of Feeblemindedness*[4]: In general, "their principal shortcoming is a greater or lesser degree of inability to comply with intellectual requirements of their society. In other respects, they may be as mature

or immature, stable or unstable, secure or insecure, placid or moody, aggressive and submissive as any other member of human species."

Until recently the interest in mental retardation was limited to professional personnel who worked in institutions. This attitude is gradually changing, primarily due to the efforts of organizations of parent groups of the retarded. They have influenced expansion of interest in care, treatment, and research in mental retardation to various professions outside of institutions. So far, however, the emphasis has been mainly on basic research into the organic causes of severe and moderate retardation and provisions for training and community residential facilities for these groups. There appears to be disproportionately little interest or programming in clinical research, particularly in the study of personalities and problems of the mildly retarded adolescent.

The writer does not intend to imply that all mentally retarded adolescents require psychotherapy. Fortunately, because of some innate traits of personality and a high psychic threshold, the majority of these people are making a satisfactory social adjustment and apparently receive enough inner satisfaction out of life in spite of all the exigencies they have to face. The plea is for the acceptance of those among them who need help, and to treat them rather than reject them simply because of subnormal psychometric ratings. From personal experience and from reviewing some of the literature, the writer does not support the notion postulated by those who believe that the mildly retarded need assistance and supervision from cradle to grave. As evidenced by the above-mentioned small study by the writer, of discharged patients, and from the history of some of our brighter patients who leave the institution to return to their own homes, it is evident that many of them are able to manage their own affairs without professional supervision.

The writer would like to close the discussion by quoting the conclusion of the study of *The Social Adjustment of Morons in a Connecticut City* by Kennedy,[7] one of the rare detailed studies of a group of noninstitutionalized mentally retarded persons in their middle twenties, made in Connecticut in 1946–1947.

> Indeed, the present author feels strongly that most, if not all, morons are unjustly designated as "feeble minded" in the literal sense. They may be subnormal in many respects, as compared with non-morons, but in many others they do not even show subnormality. Human adjustment in society is so much a matter of degree, and depends upon such a varied composite of factors, that one would find it hard to set up a rigid standard of social adequacy. This is especially true in a complex society like that of modern America. Here, so wide is the range of socially useful activities, and so diversified are the roles individuals may play in social life, that places can be found for all kinds of men, including those who are not very intelligent. One is tempted to assert, after noticing the creditable showing of morons in the economic sphere particularly, that there are many types of work in our society for which morons seem to be very well suited. Certainly the main result of our investigation is a demonstration of the social adequacy, within limitations, of the morons we studied. In their humble way most of them are worthy citizens who bear their share of the social burden and do nothing to threaten the welfare of society.

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Clinical Evaluation of the Adolescent Retardate

Harriet E. Blodgett, Ph.D.

THE SHELTERING ARMS

MINNEAPOLIS, MINN.

For mentally retarded persons we can anticipate that, at best, limitations of capacity will curtail their achievement and adjustment levels. Evaluation of adolescents in order to provide wisely for their further training is important for useful prediction. Another problem of importance is produced largely by shortcomings in terminology. The range of ability levels, social adjustment levels, learning capacities and achievement, and personality traits in adolescents all of whom might be included in the term "retardate" is tremendously broad. Without more precise definition or description of the individual, we can be sure that any generalizations we make are suspect as far as validity is concerned.

During the adolescent period, the major concerns of educators and guidance workers are with practical problems: the likelihood of self-support, the probable later capacity of the individual to manage himself and his affairs with ordinary prudence, and capacity to fit in with the world at large well enough to produce benefits both to himself and to society. Differences between two retardates of the same ability level may be very great in terms of family background, experiences and training, personality characteristics, social attitudes, and behavior adjustment.

Essentially, the most vital need for the retarded adolescent, the quality that gives him the greatest chance of community survival and adequate adjustment, is a sufficient amount of selfhood, ego strength, self-valuation to permit him to withstand many devaluating experiences, failures, and frustrations without losing his emotional balance. This capacity must be built on personal strengths rather than on achievement experiences alone, because achievement experiences throughout the childhood period cannot be expected to provide enough rewards to build up the flexible resiliency that the individual is going to need. It is the rare retardate who can excel in anything on a competitive basis with normal age mates.

For normal youngsters, adolescence is viewed as a time during which content and subject matter learning are highly important and are increasingly the youngster's own responsibility; this is a time of rapid progress toward the assumption of adult social patterns of behavior and a period during which youngsters are increasingly organizing and reorganizing their goals, selecting among their interests, and rather actively participating in planning their own futures. Historically, people working with retarded persons have argued by analogy from the education of normal children to the education of retardates; our high school level special education programs bear witness to the general thought that if something is good for normal youngsters, its equivalent or a substitute for it is equally good for retarded youngsters. This may be true for those retardates in the upper end of the ability distribution whose retardation is demonstrated principally in difficulties of academic learning and whose skills in other areas and whose general adjustment are not markedly different from

those of the normal group. Our chief problems, however, do not concern this group of retardates, but rather center around those of lesser ability having a greater number of other problems. For these youngsters, whose retardation extends into most or all areas of living, we need to consider more realistically what the role of the school can be.

We know quite well, for example, that the retarded individual as an adult will not be earning his living in an area in which proficiency with academic skills is a crucial requirement. Whatever academic skills he has been able to master may be satisfying to him, but the difference in usefulness between a second grade level of reading skill and a third grade level is probably not sufficient to balance the time, effort, and probable frustration involved in raising the reading level by this amount. We know that the retarded youngster has as one of his most important intellectual characteristics basic, genuine inability to generalize and hence has limited ability to learn vicariously or to apply and adapt knowledge to the solution of new problems. It seems important, therefore, that the educational experience of the retardate involve a wider-than-usual variety of actual concrete experiences. We know, too, from the evidence of various follow-up studies, that the crucial traits for adult retardates are such things as: motivation to work and be self-supporting; ability to get along with other people, especially fellow-workers; possession of traits of reliability, dependability, job responsibility; generally acceptable social behavior and attitudes. These are the characteristics with which professional workers need to be concerned. Attitudes of the retardate toward himself and toward other people in his social environment are of central importance.

Professional techniques of evaluation useful with the adolescent retardate are of varying precision and exactitude. In making absolute comparisons of retardates with the normal population of comparable age, we can place the greatest degree of confidence in our instruments for the measurement of intelligence and school achievement. Through the use of a variety of ability measurements, we can see some patterning of abilities and skills, i.e., motor, manual, visual, and verbal sorts of comparisons, which contributes to the "steering" of training and experiences for the individual. Some of our other tools for studying personality and attitudes are just not very applicable for use with retarded youngsters.

Their verbal limitations and difficulty in introspection and self-description limit the meaningfulness of many personality tests designed for use with normal children and adults, and their lack of skill with paper and pencil techniques interferes with the use of many self-report inventories. Tendencies to react impulsively and "on the spur of the moment" behaviorally falsify the "proper" verbal statement even though many well-trained retarded youngsters can give the socially correct response on a verbal level; the consistency between what they say should be done and what they really do in behavior is markedly poor. Some of the projective instruments, such as the Thematic Apperception Test and the Rorschach Test, can and do provide us with information about the emotional patterns and dominant drives expressed by the youngsters, but these require highly trained professional skill to give and to interpret—often not available to many retarded youngsters in school settings—and furthermore, we do not know precisely how to repair some of the emotional problems

even when they are revealed to us. It contributes to our understanding of why a retarded adolescent may be presenting social problems to know that he feels angry and hostile about the world and is highly competitive about wanting to be a "big shot," but understanding his situation does not in itself solve the problems.

There are other sorts of evaluation extremely useful in planning for retarded adolescents. The teacher is one key person in providing some evaluations, since it is she who sees the youngster against a framework of others of comparable age and ability. The teacher's special opportunity to contribute, however, may be somewhat offset by the likelihood that her frame of reference has been established for retarded youngsters so that her judgment of a "high" area may need to be relocated in terms of what is the expectation for normal youngsters. The "high" area may be high relative to the retarded group but low relative to the normal group. With this caution in mind, teachers' evaluations have much to add.

A useful summary of a retarded adolescent should include several kinds of information to contribute to planning for his future. Basically, we need a personal history summary, including whatever is known of causation of the defect, birth history, health history, family situation, family constellation and parental attitudes, cultural and educational standards of the home, school experience, school achievement, several intelligence tests of different types and at different points of the child's development, social experience. Beyond this, what is needed involves, at our present stage of knowledge, descriptions and/or ratings of the child's actual functioning in situations in which he can be adequately observed. Traits of special importance include the following.

His Work Habits. How much motivation does he show? How eager is he to learn? How goal-directed is his behavior? What satisfactions does he get from achievement? How willing is he to make effort? What are his reactions to disappointment, failure, frustration? What use does he make of information? What kinds of information interest him? What does he like to do?

His Steadiness of Independent Effort. Many youngsters who function quite well with close supervision and adult attention and guidance are unable to make a constructive effort apart from the adult supervision. This is an important trait in relationship to employability, and one with which we like to see a youngster making progress during the early adolescent years.

Habits of Emotional Expression. What outlets does he typically use for his strong feelings of anger, resentment, hostility? Does he attack directly and aggressively, or does he withdraw? When his anger is directed at people, does he show some sense of fair play or is this an indiscriminate outburst directed at whoever is in the way? Is he aware of other people's rights when he is angry, or do all rights except his own get swept aside by his wrath of the moment? How easily irritated is he? What sorts of things make him angry?

General Behavior Controls. Even when under no specific emotional strain or situational demand, how well controlled is he? When he has no specific assignment at the moment, does he lapse quickly into randomly hyperactive or restless behavior or can he maintain a semblance of calm even when not constantly occupied with prescribed things to do?

Outward Social Skills. How comfortably can he react to new people and new social situations? How adequate are his communication skills? How well can he express himself? How acceptable is his language? Can he control it when important to do so? Can he converse with people in general without being labeled as too "different"?

General Capacity to Take Self-responsibility and "Look After Himself." Can he stay out of trouble? Can he occupy himself reasonably well without constant direction? Can he keep a promise? Does he have useful and acceptable interests for leisure time and otherwise unoccupied periods? Can he avoid involvement with undesirable behavior? How suggestible is he to others? How likely is he to be victimized by others?

Interest in Sex, Developing Patterns of Sexual Behavior. Previous studies indicate that problems of sexual delinquency are more frequent among retarded girls than among retarded boys, although of course this may simply mean that the results are more obvious for the girls and hence the problem attracts greater social concern. Needs for affection, attention, and approval are often cited as factors in sexual delinquency, suggesting that more effective general experience might act as a deterrent. For both boys and girls, however, sexual interest and behavior are important factors in determining community adjustment.

Experiences in prevocational training centers indicate that retarded adolescents preparing for work still need a considerable amount of help in learning to meet conventional standards of grooming, self-care, personal appearance. This need may stem from long-continued parental overprotection, which has failed to make possible a transition to a period in which the adolescent takes self-responsibility in this area, or it may reflect some failures of educational provision, or it may also involve the adolescent's increasing awareness of his own "differentness" and sensitivity to this. His feeling of inadequacy in the "external" area may really be a projection of a more important feeling of inadequacy internally with regard to his abilities and skills.

As we think ahead to problems of community adjustment of retarded adolescents as they become adult and move into the world of work, there are two major ways in which the adult models of the culture assume an important role. In general, the middle class population has a "striving" sort of attitude and wants to move ahead and upward vocationally and socially. The normal ability child of a lower class family often has conflicts as he discovers that values of his family differ from values "recommended" by his school experiences. The retarded child, however, is likely to find himself not just conflicted but completely blocked if he rejects and looks down on the kinds of work he is able to do.

The attitude of liking to be useful and to do useful things is a most important attitude for the retarded child to learn. It is important that parents do not devaluate routine sorts of work in an attempt to instill ambition in their retarded child. Respect for work, as work, as needing to be done, taking for granted the need to work, learning to enjoy the process as well as the rewards of the process, all are part of the growing-up experiences that have special importance for the retarded youngster. The processes of building in retarded children the desirable attitudes

and habitual responses that will make possible for more of them successful lives in the community are facilitated by a more widespread understanding of the desired goals and the possible outcomes. The two major factors that contribute to desirable, or undesirable, outcomes are, first, the family atmosphere and, second, the educational experience.

The family atmosphere for the retarded child is likely to be clouded for some years in confusion, conflicted feelings, alternating overpressure and overprotection, plus the myriad other emotional reactions that parents feel and show when informed of a diagnosis of mental retardation. Although parents will still differ in their capacity to accept and cope with the problems of bringing up a mentally handicapped child, there is considerable evidence to support the view that more adequate interpretations to parents, plus closer working relationships between school and home during the childhood years, contribute to better handling of the situation by parents and to decreased conflict between parents and child emotionally.

Perhaps it is the educational experience over which we have the most direct control. School programs can be built to contribute to the development of optimum emotional health and the inculcation of socially useful and constructive attitudes. Whether they are so built, or not, depends largely on how clearly professional workers are able to think realistically about the goals of school experience for retarded children and to separate these goals, when necessary, from the conventional purposes of education. Whereas with normal children school attendance is designed to impart information and the tools for learning in an atmosphere that also facilitates social development and desirable adjustment, for retarded children possibly the goals of school need to be reversed; it is of the highest importance that desirable adjustment and favorable social behavior patterns be established, whereas the role of information and the tools for learning are of secondary importance in terms of long-range needs.

Of factors that contribute to the development of emotionally healthy personalities, we recognize as being among the most important: family security and acceptance; the development of some skills and achievements that bring satisfaction to the individual; enough success experiences to contribute to ego strength and personality resiliency so that some failures can be absorbed without undue damage to personality; some appreciation of justice, fair play, and the rights of others so that rules and regulations can be better tolerated.

Even with normal adolescents, our methods of evaluation are far from complete or perfect. Levels and patterns of adjustment change over the time dimension; the well-adjusted child at the age of 10 is not always the well-adjusted adolescent at the age of 15, nor does the well-adjusted adolescent always prove able to maintain this adjustment level into maturity. While it is true, in general, that past behavior offers the best prediction of future behavior, it is also true that, during the developmental years, growth and maturation introduce new variables into the equation of behavior prediction. One function of school, during the adolescent years, may be simply to "hold" the child in a psychologically healthy setting while maturation does its work of preparing him more fully for adult living. We may have tried too hard to keep retarded children in school programs beyond their ability to profit

from the material offered when, from the viewpoint of their total needs, general work experience would have been more to the point. If this is so, then the task of the school is to provide, within a school framework, prework training rather than continued academic content. We are familiar with the leveling-off process of mental growth in the mentally retarded person. Possibly this is paralleled by a leveling-off process of social growth also, which suggests some point in earlier job placements or combinations of job training with school settings.

In summary, evaluation of the adolescent retardate is composed of several elements representing both measurement and judgment. Measurement is possible and useful in areas of ability, ability patterning, achievement; judgment is necessary in areas of social skills, attitudes, patterns of emotional expression. Evaluation should also include consideration of the effect of past experiences on present adjustment, particularly the influences of home and parental attitudes and practices and those of previous school experiences. Better social planning for retardates will in the future stress some goals of education that differ from those held for normal children and will be centrally concerned with the development of personality and emotional strengths and social acceptability and desirable attitudes toward the social world of the retardate.

Temporal Bone Banks

Five temporal bone banks to aid research on hearing loss have been established in the United States during the past year by the Deafness Research Foundation. The banks are at Columbia University, College of Physicians and Surgeons, New York University Medical Center, Johns Hopkins University School of Medicine, University of Chicago, and University of Michigan. The banks are directed by the head of the department of otolaryngology at each university.

The Foundation has made a national appeal for persons to bequeath their temporal bones for investigative research into deafness. Most useful are bones from persons who have suffered deafness from various causes; also required are bones from normal persons to aid physicians in perfecting surgical techniques.

The Metabolic Basis of Some Inborn Intellectual Disorders in Adolescents

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CLINICAL CHEMISTRY OF MENTAL RETARDATION

Gene Defects. Thudichum (1884) was the first to evaluate cerebral disorders in terms of chemical mechanisms, stressing the dominant role of brain lipids in intellectual function. Garrod (1923) described some inborn errors of chemical metabolism, none of which involved mental retardation. More recently, several clinical disorders have come to light as inborn biochemical specificities with mental defect as a by-product. Some of these inherited disorders, such as galactosemia and phenylketonuria, reveal mental deficiency in early infancy, whereas others, such as gargoylism and lipidosis, reveal mental deficiency as the end result of metabolic defect. The inborn metabolic error is a permanent inherited condition due to a primary enzyme abnormality. It is a biochemical lesion responsible for the disordered cerebral metabolism that leads to visible tissue damage throughout the body. One or more chemical compounds may thus follow an altered metabolic pathway and appear in body fluids in greatly increased or decreased amount. Himwich et al[59] demonstrated reduced cerebral metabolism in mongolism, cretinism, phenylketonuria, microcephalus, hydrocephalus, and amaurosis, and normal cerebral metabolism in other severe amentias.

An inborn error of metabolism is caused by an abnormal gene present at the moment of conception. It becomes manifest as an isolated enzyme defect in some organ of the body even though the genetic abnormality is transmitted to every cell in the body during cell multiplication and organ differentiation. For example, in galactosemia, the disease is manifest as a form of liver dysfunction due to an enzyme defect, yet the red cells show the same defect since the disease is generalized. There are two kinds of hereditary dispositions to metabolic error: One type is almost always genetically homozygous, the affected child lacking an enzyme because the abnormal genes present in duplicate fail to produce it, although a carrier with one abnormal and one normal gene is still able to synthesize the necessary enzyme. The second type of metabolic defect revealing dominant inheritance is less regular in its effect in leading to manifestations precipitated by marked stress or environmental circumstances, conducive to some of the common psychoses. A rapidly gro ving group of intellectual disorders thus represents inborn errors in chemical metabolism with mental deficiency as an accompaniment of systemic derangement.

Genes influence enzyme formation; hence an alteration of a gene retards or prevents enzyme synthesis. Enzyme catalysis is slowed or eliminated with consequent block in cell metabolism in persons homozygous for the mutant gene. Some compounds tend to accumulate and others fail to form, causing diverse disturbances in different tissues of the body. Galactosemia and phenylketonuria not only represent such

blocks in metabolism, but the unique role of nutrient factors in precipitating the disease, e.g., elimination of galactose in galactosemia and phenylalanine in phenylketonuria, alleviates the inborn disorder without altering the genetic make-up of the individual or replacing the missing enzyme.

Genes also influence protein synthesis and therefore enzyme structure, which is protein in nature. In sickle-cell anemia a mutant allele is responsible for the synthesis of abnormal hemoglobin Hb-S, whereas in other hemoglobinopathies, single genes are responsible for each of the different types of hemoglobin. Smithies (1955) demonstrated three groups of haptoglobins in the plasma of normal persons determined by two allelic genes. In hepatolenticular degeneration, Scheinberg et al (1952) identified ceruloplasmin as the abnormal protein in plasma. In hemophilia, Brinkhaus (1953) demonstrated a defect in the formation of antihemophilic globulin, a normal component of plasma essential for blood clotting. Inherited disease is a heterogeneous problem in that a single clinical disorder usually turns out to be a complex of different entities with enzyme deficiencies occurring at separate points in metabolic sequence. A specific abnormal gene has thus far been demonstrated by Cori (1954) for glycogenosis, by Harris (1955) for refractory rickets, by Codounes (1952) for methoglobinemia, by Millman et al[102] for gargoylism, by Dent et al[36] for cystinuria.

Biochemical Lesions. Biochemical or physical trauma to the developing fetus produces various forms of amentia without impinging on the fetus because its defective metabolism is compensated by normal maternal mechanisms. Even the enzyme defect phenylketonuria is compensated by the transfer of maternal substances via the placenta, i.e., excessive phenylalanine diffusing across the placenta is oxidized by the maternal organism. Defective or deficient substances in other forms of amentia may be supplied to the fetus by the maternal mechanism via placental diffusion. Metabolic defects must be corrected, however, shortly after birth to maintain adequate mental function and prevent mental degradation. Ingalls (1956) confirmed the author's[89] observations that the time of fatal injury in the course of embryonic development is determinative of the type of congenital defect rather than the nature of trauma. But severe types of amentia, such as encephalocele, resulting from early fetal trauma cannot be compensated by the maternal organism, hence the need for special preventive measures indicated during critical periods of embryonic development.

Mental deficiency arising from any cause involves cerebral dysfunction from interference with higher central nervous system activity. It reflects the caliber of the neuronal impulse derived from oxidative reactions and stored in the form of high energy organic complexes. Interference with substrate oxidation or utilization of the resulting energy impairs cerebral cells or intellectual function. Fazekas (1958) found the basic requirements for energy production and utilization by cerebral cells to involve glucose as a source of energy, oxygen for carbon dioxide and water, enzymes and coenzymes for catalyzing the degradation of glucose, and effective mediation of interneuronal impulses.

Glucose deficiency results in cerebral dysfunction and, if marked, in structural injury. Reduction of cerebral blood flow will not deprive the brain of its glucose

supply because of the abundance of glucose in the blood, but decrease in blood glucose concentration will reduce cerebral glucose below critical levels. Oxygen deficiency is a determining factor in cerebral dysfunction because glucose degradation requires a large and continuous supply of O_2 from the blood circulation. Kety (1948) found the normal O_2 consumption of an adult to be 50 ml./min. or one fifth of the total oxygen consumption of the entire body and the blood flow to be about 800 ml./min., one sixth of the total cardiac output. The O_2 content far exceeds cerebral requirements; hence there is a considerable margin of safety in moderate hypoxia or in reduced cerebral blood flow. Protection is afforded by regulatory mechanisms involving cerebral vasodilation and increased vascular resistance. Cerebral hypoxia is usually the result of local circulatory or systemic disturbances. Rossen (1943) demonstrated that total interference with O_2 supply to the adult brain produces irreversible cortical damage in five to eight minutes.

Enzyme and coenzyme defects interfere with aerobic and anaerobic reactions involved in cerebral energy production. Primary enzyme inhibition rarely produces irreversible brain injury in spite of depressed cerebral O_2 utilization because the metabolic needs of cerebral cells are diminished in enzyme deficiency as long as enzyme-regenerating structures retain their activity. Sebrell (1953) demonstrated the role of the B complex vitamins in coenzymes for energy production, thiamine as a cocarboxylase in the carboxylation of keto acids, riboflavin as a constituent of flavoadenosinediphosphate and flavine mononucleotide for regulating oxidation-reduction of fumaric and succinic acids, panthothenic acid in the structure of CoA, niacin as a component of diphosphopyridine neucleotide and triphosphopyridine neucleotide for oxidation-reduction in the carbohydrate cycle, pyridoxine in deamina.ion and transamination of 5-hydroxytryptophan decarboxylase essential for serotinin synthesis.

Drugs inhibit enzyme systems and impair cerebral function by inhibition of the enzyme or coenzyme, by binding its active radicals, or by denaturation of its protein moiety. Increased carbon dioxide tension of the blood produces cerebral dysfunction owing to the cerebro-dilating effect with a rise in arterial carbon dioxide tension exceeding 4 mm. of mercury. But carbon dioxide retention produces depression, anxiety, irritability, confusion, delirium, and coma. Marked reduction in carbon dioxide tension produces cerebral dysfunction, especiallv dizziness, impaired memory, disturbed consciousness, and oral paresthesia. Hypocapnea in hyperventilation is accompanied by reduced cerebral blood flow. Finnerty (1954) attributed these manifestations to uncoupling or to interference with enzymes sensitive to changes in carbon dioxide tension.

The diagnosis is nearly always a comparatively simple matter apart from the family history because the inborn error often reveals wide deviations from the normal. The clinical picture may vary from complete normality to acute attacks of the disease, to long-standing chronic disease, or to a slowly developing disease at any time of life. These variable manifestations indicate that the genetic defect is not directly harmful but acts only to predispose to a disease precipitated by an environmental cause, e.g., in galactosemia there is an abnormal sensitivity to dietary galactose; in phenylketonuria, to phenylalanine; in Hartnup disease, to light. The

clinical features thus vary with the nature of the environment, which should give the proper lead for early recognition and treatment of the specific intellectual disorder. Intelligence at the borderline and moron levels represents the chance accumulation of normal genetic factors; hence it is not truly pathological. But suppression of intellectual development by genetic and environmental forces leads to pathological mental retardation. Specific types can be separated from the large heterogeneous group of undifferentiated aments only by the presence of an associated biochemical or physical abnormality.

INBORN ERRORS OF BODY STRUCTURE

Clinical Teratology. Experimental studies reveal fundamental principles involved in prenatal malformations but no direct applications to the pathogenesis of mental malformations. Each pattern of malformation has for its inception a critical period in which the neuroblasts of the affected region become vulnerable because of increased metabolic activity at that time. All experimental work indicates that, whatever the effective noxious stimulus to the developing ovum, it is the stage of development at the time of the experiment that is decisive. Hicks[57] constructed a timetable of predictable malformations in experimental animals subjected to a single dose of ionizing radiation, correlating the stage specificity of the changes with the phases of accelerated metabolic activity of the neuroblasts that involved increased formation of nucleic acids and proteins. Administration of enzyme inhibitors such as sulfhydryl compounds produced similar malformations. The immature brain however possessed considerable power of recovery after injury for some damaged areas often showed complete restoration to normal.

The neuroblast is more resistant to anoxia and hypoglycemia than the mature nerve cell. Muskett[104] showed that the more rapidly differentiating structures were more vulnerable when oxygen deficiency reached critical levels. Hicks[57] observed that anoxia in later fetal life produced severe brain damage from vascular injury and anemia infarction. Hallovorden[51] reported cerebral destruction in an infant born of a mother who attempted suicide by coal gas inhalation. Engler[44] correlated lack of oxygen or other nutritional deficiency with faulty implantation of the ovum, which led to mongolism and other types of malformation. Irradiation during the early months of pregnancy invariably produced microcephaly, mongolism, and other developmental defects in the offspring. Woollam et al[141] produced hydrocephalus in experimental animals whenever the mother was deprived of vitamin A for five months before mating. The time of injury, the nature of the offense, and the extent of the repair determine the ultimate form of an anomaly, without indicating precisely the developmental stage of onset of the abnormal process.

Genetic factors dominant for common malformations recur in the same form in the same family. Record et al[112] found the chances of malformation in forthcoming progeny to be nine times the average expectation, especially in advanced maternal age and excessive pregnancies. Penrose[106] found simple Mendelian inheritance in but few instances, for the mutation rate would have to be unusually high if fresh mutations were responsible for keeping these lethal anomalies in equilibrium.

Maternal infections other than syphilis pass the placenta and interfere with the development of the offspring. Swan[123] found that more than 93 per cent of mothers with maldeveloped progeny had been infected during the first four months of pregnancy, whereas Lündstrom (1952) found an incidence of only 17 per cent; hence teratogenic virulence of the virus varies in different epidemics. The commonest malformations were microcephaly, hydrocephaly, deafness, cardiac defects, epilepsy, and spastic syndromes. Kass[76] correlated hydranencephaly with infectious hepatitis in the mother; Diezel,[38] micropolygyria and cytomegalic inclusion body disease with maternal infection during the fourth month of pregnancy; Wyatt et al,[143] toxoplasmosis with maternal infection during the latter stages of fetal life; Crosby et al,[28] congenital hydrocephalus with staphylococcal infection of the mother.

Congenital Malformations. Craniosynostosis represents fusion of one or more cranial sutures as a hereditary defect occurring in ancestors and siblings with consequent deformities of the skull, limitation of brain growth, and eventual mental retardation. It is characterized by cranial deformity, prominence of the eyes, papilledema, amentia, and convulsions. Roentgenograms of the skull during the first months of life enable surgical correction of the defect before amentia develops. Synostosis of the coronal suture produces less mental retardation than synostosis of the sagittal suture.

Hydrocephalus is an intracranial anomaly, lesion, inflammation, or neoplasm, which interferes with the circulation or absorption of cerebrospinal fluid causing dilatation of the cerebral ventricular system by increasing intraventricular pressure. It is characterized by bulging fontanel in the upright position, downward displacement of the eyeballs, vomiting, irritability, somnolence, motor disturbances, and spasticity of the lower extremities. Rapid enlargement of the head occurs in Schilder's disease, Hurler's disease, and lead poisoning. Surgical intervention is determined by the underlying cause of the hydrocephalus. The arachnoidureteral shunt in particular causes an obligatory loss of electrolytes, especially NA^+ and Cl^-, in the urine; hence addition of 2 Gm. of salt per day to parenteral fluid maintains the required electrolyte balance and prevents needless fatalities.

In microcephaly, a markedly diminished head circumference is not the determining diagnostic criterion; hence Böok[17] suggested that the child's skull should be three standard deviations below the mean for the age, not due to premature synostoses of the cranial sutures. The condition may be induced by maternal pelvic irradiation, prenatal infection, or birth trauma. Microcephaly is usually of genetic origin unless proved otherwise because of the 25 per cent recurrence risk in affected families.

Acrocephaly is a mild mental deficiency accompanied by a prominence of the central region of the skull, beaklike nose, exophthalmos, and exotropic prognathism. Falls (1953) demonstrated its transmission by a dominant gene with fairly high penetrance, but sporadic cases may occur by new mutations. Acrocephalosyndactyly or Apert's syndrome is a form of amentia characterized by a towering skull, flattened enteroposterior hypertelorism with broadened forehead, and syndactyly of the fingers and toes, inheritance being regulated by a dominant gene and some pedigrees, by recessive inheritance.

Congenital heart disease with right-to-left shunt accompanied by cyanosis and

polycythemia is a threat to cerebral integrity and maturation. Thrombosis of the cerebral artery is invariable in hot weather as a result of hemoconcentration, minimized by the maintenance of a high fluid intake. Cerebral injury may, however, be induced by dehydration accompanied by intravenous pyelography. Ingraham (1954) demonstrated the passage of infected emboli from the lungs to the brain with consequent cerebellar abscess formation. Cerebral injury is manifest by headache, vomiting, fever, and focal neurological and electroencephalographic signs despite relatively normal cerebrospinal fluid in the early stages.

Arhinencephaly was described by Rasmussen[111] as a mental deficiency accompanied by absence of the olfactory bulb and tracts and their associated structures and attributed by Grebe[49] to a dominant gene with variable manifestations since relatives appeared slightly affected.

Mongolism presents more than 25 diagnostic signs, but Penrose[106, 107] considered seven stigmas essential for the diagnosis: intelligence quotient 15 to 30, cephalic index 0.84 or higher, epicanthic folds over either eye, fissured tongue, blepharitis, transverse fold on either palm, single flexion crease on either little finger. Walker[136] advanced an objective method of diagnosis from dermatographic analysis. There are no characteristic changes in the brain and no significant endocrine or metabolic disorders. A genetic factor makes some families particularly susceptible to the disease. Mongoloids reveal cerebral degeneration, cortical atrophy, and loss of nerve cells, yet the rate of O_2 consumption is normal until age 19 years, when the cerebral A-V O_2 difference ceases to rise. Himwich et al[58] observed 5.6 vol./100 ml. in adult mongoloids in comparison with 6.7 vol. in normal adults attributable to the early arrest of vital components of the cerebral respiratory system.

Ectodermoses include tuberous sclerosis, neurofibromatosis, and cerebral angiomatosis due to inborn neoplasia or dysplasia in the central or peripheral nervous system and in other organs. Mental deficiency accompanies convulsions, skin manifestations, and osseous defects.

INBORN ERRORS IN PROTEIN METABOLISM

Phenylketonuria.

PHENYLPYRUVIC AMENTIA. Phenylketonuria is primarily a hepatic disorder and secondarily a severe mental deficiency. It is transmitted by an autosomal recessive gene and induced by absence or inactivity of L-phenylalanine hydroxylase in the liver that fails to oxidize phenylalanine to tyrosine. Kenny et al[77] showed that all newborn infants lack hepatic phenylalanine hydroxylase, which normally appears several weeks after birth in response to specific intestinal stimuli. But such stimulation produces the inactive enzyme in the phenylketonuric; hence it takes two to six weeks for phenylketonuria to be detected. Phenylpyruvic acid can be readily identified before the onset of mental and neurological manifestations. Addition of a few drops of 5 per cent ferric chloride or 2,4-dinitro-phenylhydrazine solution to the urine gives a bluish green color, which fades within a few minutes, but false positives are formed by salicylate, diacetic, pyruvic, or homogentisic acid. A diaper with a freshly voided urine may be tested in the same manner. Phenistik is an impregnated filter paper that gives a green color when dipped into urine con-

taining phenylpyruvic acid. A confirmatory rise of plasma l-phenylalanine above the normal 1.0 mg./100 ml. establishes the diagnosis in an infant after the first month of life. Kugelmass[89] advocated routine urine examination for phenylpyruvic acid in retarded infants and in the siblings of phenylketonurics.

A normal blond, allergic infant with blue eyes and fair skin reveals slow mental development from the early months of life. The fetus is usually protected by maternal enzymes; hence abnormalities develop months after birth. Serum phenylalanine concentration is normal at birth; hence the signs of phenylketonuria begin to develop during early infancy. Accentuation of both superficial and deep tendon reflexes is correlated by electroencephalogram showing a long RSP complex with multiple seizure foci. Both the infant and his urine gradually acquire a penetrating musty odor of phenylpyruvic acid, which calls attention to the disorder before amentia becomes evident by the sixth month. Fölling[46] observed reduction in head measurements, diminution in body size, dilution of hair and skin pigmentation, and accentuation of all reflexes. The fair coloration of the hair and skin and the blue eyes occur in 90 per cent of the aments. Cowie et al[26] compared the pigment dilution with the coloring of other members of the family by reflectance spectrophotometry. Miyamoto et al[103] demonstrated that circulating L-phenylalanine in phenylketonuria inhibits the tyrosine reaction, interferes with melanin formation, and causes skin pigmentation. The light skin is susceptible to trauma, irritation, and eczema and reveals dermatographia, photosensitivity approaching albinism, increased sweating, and a body odor of phenylpyruvic acid. The gait is short, stiff, jerky, the posture kyphotic or semirigid, the motion stereotyped, but all neurological signs are nonspecific. One half of the affected children never learn to talk, one third never learn to walk, but the rest are trainable and educable. Alvord et al[1] demonstrated diffuse demyelination with neurological signs in two thirds of the aments, especially hyperactivity of the deep reflexes, muscular hypertonicity, ataxia, athetoid movements, tremors, and restlessness in repetitive motion. Grand mal seizures decrease with age in one fourth of the children.

Parents with one phenylketonuric child will probably produce another with the same condition, with a 25 per cent probability for each pregnancy. But two out of the three normal siblings will be carriers. Hsia[63] detected 1 in 66 heterozygous carriers but 1 in 20,000 phenylketonuria carriers, and he identified the carriers by the phenylalanine tolerance test. Oral administration of 0.1 Gm. l-phenylalanine per Kg. body weight after an overnight fast yields twice the plasma phenylalanine levels at 1.2 and 4 hours after the test dose in heterozygotes than in normal controls. Knox et al[86] found that normal siblings are not likely to have defective children because the chance of marrying carriers is slight since 1 of 100 in the general population is a phenylketonuria carrier of the gene. But marriage of normal siblings to a cousin is potentially dangerous because of the great predominance of the recessive gene in relatives. Jervis[73] found 1 per cent of aments to be phenylketonic in this country; Munro (1957), more than 2 per cent in England; Wright et al,[142] the disease in all races. The gene for phenylketonuria is not truly recessive but is an incompletely dominant one, which expresses itself to some extent in the heterozygote and to a marked extent in the homozygote.

BIOCHEMICAL LESION. Phenylketonuria is characterized chemically by a high level of phenylalanine in the blood, cerebrospinal fluid, and urine of affected aments up to 40 times normal, reflecting a marked disturbance of aromatic amino acids in general and of phenylalanine in particular. Armstrong et al[4] found the plasma phenylalanine to be 15 to 60 mg./100 ml., in comparison with the normal 1 mg./100 ml.; Borek et al,[18] cerebrospinal fluid phenylalanine about 7 mg./100 ml., representing an increase over the normal comparable to that observed in blood; Stein et al,[121] urinary phenylpyruvic acid, phenyllactic acid, and phenylacetylglutamine about 0.5 to 2.0 Gm./day, phenylalanine excretion 0.2 to 0.4 Gm./day, and phenolic acid and indole derivatives in smaller amounts. Woolf (1950) estimated the urinary content of these substances to be about 2 Gm./day as a function of diet and body size. Armstrong et al[4] also isolated o-hydroxyphenylacetic acid up to 0.4 Gm./day and indolylacetic acid up to 0.15 Gm./day; Pare (1957), excretion p-hydroxyphenyllactic and p-hydroxyphenylacetic acids increased and 5-hydroxyindolylacetic acid diminished.

Phenylalanine is an essential amino acid whereas tyrosine is not essential, though a limiting factor for growth if the diet lacks phenylalanine. Tyrosine can thus be formed from phenylalanine but the reverse does not maintain. Udenfriend et al[127] found the aqueous enzyme system in human liver preparations responsible for the irreversible oxidation of phenylalanine to tyrosine. Later, Udenfriend (1953), using labeled phenylalanine, concluded that either phenylalanine hydroxylase activity in the liver is decreased or that the enzyme is absent, since small amounts of tyrosine are formed by an alternative pathway or by intestinal bacteria. The hydroxylation of aromatic compounds by a nonspecific mechanism probably accounts for the slow leakage of phenylalanine to tyrosine in the phenylketonuric. Armstrong et al[3] explained the excretion of indole compounds by a disturbed tryptophan metabolism.

Phenylalanine or phenylpyruvic acid feeding increases blood tyrosine in the normal but not in the phenylketonuric child. But after tyrosine feeding, Jervis[70] observed a rise in both normal and phenylketonurics, indicating a block in the conversion of phenylalanine to tyrosine. Later Jervis[71, 72] showed that a high-protein diet increases while a low-protein diet decreases excretion of phenylalanine, phenyllactic, and phenylpyruvic acids in phenylketonurics. Most amino acids produce no change in these compounds but phenylalanine feeding increases the excretion of the keto- and hydroxyacids as well as phenylalanine, and phenyllactic and phenylpyruvic acid feeding increases the blood levels and urinary excretions of these compounds. The metabolic disorder thus involves hydroxylation of phenylalanine and intraconversion of phenylalanine and phenyllactic and phenylpyruvic acids. Irreversible conversion of phenylalanine to tyrosine is the first step in the oxidation of phenylalanine derived from dietary or tissue protein. A defective enzyme system involved in this conversion leads to a block in the intermediary metabolism at this point. Consequently, phenylalanine accumulates in the blood and cerebrospinal fluid and is excreted in abnormal amounts in the urine. But phenylpyruvic and phenyllactic acids and phenylacetylglutamine are readily excreted since their renal threshold is low, relatively little remaining in the blood. Jervis (1947) demonstrated the metabolic block, confirmed by Udenfriend (1953), to be either partial or complete. The enzyme system is present in water-soluble fractions of liver but not in other

tissues and appears to be specific for L-phenylalanine. Mitoma (1956) detected two protein fractions in the enzyme—one labile, peculiar to the liver, and the other stable, occurring in other tissues. Both protein fractions are necessary for the hydroxylation, the reaction requiring both reduced diphosphopyridine nucleotide and O_2. Wallace (1957) observed no enzyme activity for the labile fraction in phenylketonuric livers in comparison with controls.

The metabolic lesion is not limited to an enzyme defect in the hydroxylation of phenylalanine to tyrosine. There are increased amounts of o-hydroxyphenylacetic acid and other derivatives formed from phenylalanine. Udenfriend (1955) showed that o-hydroxylation cannot be produced by the para-directing phenylalanine hydroxylase. Other hydroxylation mechanisms come to the fore when phenylalanine accumulates in excess. Dalgliesh[33] demonstrated this mechanism in vitro and suggested its occurrence in vivo to account for the abnormal hydroxylative compounds detected in phenylketonuria. Excessive excretion of the tryptophan derivatives, i.e. indolylacetic and indolyllactic acids, and diminished blood levels of 5-hydroxytryptamine, and diminished urinary 5-hydroxyindole acetic acid are secondary phenomena, which clear with low-phenylalanine diets. The metabolism of the entire body is altered by the loss of phenylalanine hydroxylase activity. Christensen[25] found that excessive phenylalanine in the tissues disturbed the cellular amino acid balance and the serum β-lipoprotein level. Dalgliesh[33] correlated the subnormal melanin pigmentation and epinephrine sensitivity with the products of tyrosine metabolism derived from the neural crest. Armstrong et al[5] attributed the involvement of CNS, skin, and adrenal medulla to the similarity of their chemical functions. Bickis (1957) showed that both L-phenylalanine and phenylpyruvic acid interfere with tyrosine metabolism and therefore with the production of catecholamines and other hormones from tyrosine.

The mental defect is attributed to the toxic action of the various metabolites produced in excess as a result of the metabolic block. But Borek et al[18] observed no correlation between intelligence quotient and the plasma phenylalanine or phenylpyruvic acid levels. Indeed, a child with high serum phenylalanine may be mildly retarded while one with little serum abnormality may be markedly retarded. Himwich et al[58] attributed mental impairment to the decreased removal of oxygen from the brain; Udenfriend,[128] to phenylethylamine, a phenylalanine metabolite, 20 to 60 times normal concentration interfering with normal learning or imprinting and causing irreversible effects on the brain. There is no single toxic compound liberated in the disordered phenylalanine metabolism to account for the mental defect. Quastel (1960) demonstrated phenylalanine inhibition of tyrosine essential for normal cerebral function; Knox et al,[86] excessive phenylalanine in disturbed cellular amino acid balance detrimental to cerebral function; Pare (1957), decreased 5-hydroxytryptamine the cause of the mental defect. Amentia predominates between 5 months and 5 years, during the critical period for biochemical maturation of the brain when myelination is most sensitive to excessive phenylalanine. Failure of tryptophan to dissociate into serotonin decreases serum levels and depletes CNS of serotonin, indispensable in brain function. Other p-hydroxylated substances, i.e., epinephrine and thyroxine, are equally essential for mental processes. Homeostatic imbalance

may further affect cerebral function, e.g., decreased A-V oxygen difference, abnormal electroencephalographic activity, and aberrant behavior.

Chemical Therapy. Early diagnosis enables therapeutic suppression of CNS symptoms while working against time. Low-phenylalanine diet tends to correct biochemical abnormality, amino acid imbalance, and tyrosine deficiency without nutritional stress. Kugelmass[89] showed the ineffectiveness of tyrosine, niacin, and thiamine supplementation. Bickel et al[13] used casein hydrolysates devoid of phenylalanine (Lofenalac or Ketonil) in an otherwise adequate diet to maintain a positive nitrogen balance with low blood phenylalanine levels. Woolf (1955) maintained phenylketonurics on diets yielding sufficient phenylalanine, 15 mg./Kg. body weight, to allow normal protein synthesis and growth and limit phenylalanine levels in the plasma and abnormal metabolite excretion in the urine. Berry (1958) limited phenylalanine intake in normal low-protein diets with little success because of loss of body protein, arrest of growth, and flooding of the tissues with phenylanine released from body protein. Paine (1957) found that adequate control depended on fulfilling minimal phenylalanine and optimal caloric needs. Lange (1957) provided minimal phenylalanine in about 30 mg./Kg. body weight per day in measured milk intake, supplemented by adequate calories from carbohydrate and fat, as well as minerals and vitamins. Blainey (1956) observed that a high caloric intake exceeding 100 cal./Kg. body weight per day is associated with less efficient utilization of free amino acids than of whole proteins. Optimal regulation is possible with repeated plasma or urine phenylalanine measurements.

Low-phenylalanine cereals include tapioca and cornstarch; fruits, apple, banana, cranberry, grapefruit, orange, peach, pineapple, raspberry, strawberry, and tomato; vegetables, carrot, celery, squash, and turnip; sugar and butter. Multivitamin and ferrous sulfate supplements are essential. Plasma phenylalanine levels are kept below 3 mg./100 ml. according to monthly evaluations. Hsia (1958) found that phenylpyruvic acid excretion is not a criterion since the acid disappears from the urine when plasma phenylalanine levels fall below 10 mg. Most of the disease manifestations cleared within a month after early introduction and continuous maintenance of the regime but normal intelligence has yet to be produced. Treatment initiated before the end of the first year doubled an intelligence quotient of 30 within two years of rigorous dietary regulation, but treatment begun beyond the second year increased intelligence quotient slightly, but improved emotional stability. Horner (1957) prevented intellectual impairment during the first year and reversed recently established impairment but not advanced mental retardation in older patients.

All clinical signs and biochemical lesions of phenylketonuria may be reversed completely within several months but the mental defect only partially. The diet is gradually supplemented with milk or other protein foods to provide 20 mg. phenylalanine per Kg. body weight instead of the normal 200 mg. Armstrong (1957) observed a decrease to normal urinary levels of phenylalanine, phenylpyruvic acid, o-hydroxyphenylacetic acid, phenylacetylglutamine, phenyllactic acid, indolyllactic acid, and indolylacetic acid; Pare (1958), a rise in blood serotinin, clearance of the peculiar odor of the urine, but no change in urinary 5-hydroxyindoleacetic acid; Brown et al,[22] disappearance in half the cases of the abnormal components accom-

panying plasma β-globulin and restitution of the β-lipoprotein patterns. Neurological signs are ameliorated except for structural defects and brain damage. Hsia (1958) reported favorable effects on behavior and attention span. Lange (1957) precipitated continuous seizures during the first week of treatment in several cases due to severe hypoglycemia but continued therapy gradually eliminated the seizures and normalized electroencephalogram except in children with severe neurological defects. Hair-darkening can also be effected without lowering phenylalanine by increasing tyrosine uptake to overcome the competitive inhibition of tyrosinase by phenylalanine.

Hartnip's Disease.

Tryptophan Amentia. Mental deficiency accompanied by physical and neurological manifestations of classical pellagra is a primary disorder of tryptophan metabolism or amino acid transport systems with a secondary renal tubular defect inherited as an autosomal recessive. Baron et al[6] named the disease after a family with two affected offspring of a consanguineous marriage and Henderson[55] confirmed it in another case. One child showed temporary cerebellar ataxia, hereditary dermatitis, and renal aminoaciduria; and the other, mental confusion, nystagmus, aminoaciduria, and polyuria. The initial complaint referred to the red, scaly pellagra-like rash that became dry, raw, and blistered intermittently over parts of the skin exposed to sunlight. It was accompanied by neurological manifestations with severe but reversible cerebellar ataxia manifest at the height of the skin rash or after an infectious disease without a rash. The presence of a photosensitive skin from birth ruled out pellagra and favored a pure cerebellar ataxia with occasional traces of pyramidal signs. Attacks were precipitated by fever, sulfonamide, and emotional stress, especially on a niacin-deficient diet. The neurological picture varied, revealing ataxia, nystagmus, double vision, ptosis, and increased deep tendon reflexes. There were involuntary movements of the tongue, intention tremor of the hands, disturbance in all fine movements, and unsteady gait. The ataxia developed suddenly reaching a peak within a day or two and gradually subsided over a period of weeks. Weyers (1958) observed recurrent fainting attacks and persistent headaches. Mental disturbance ranged from mild emotional instability to complete delirium simulating classical pellagra. Mental retardation was manifested by gradual increase in dulled responses, aberrant behavior, and nervous irritability.

The diagnosis is established from the chromatographic pattern of excreted amino acid, more significant than total amino acid or excessive indolylacetic acid and indican excretion. The remarkable feature is the relatively constant pattern in each patient throughout life. Milne (1959) used oral tryptophan loading accompanied by paper chromatography to reveal the abnormal response in serial samples. H disease should be suspected in pellagra not due to dietary deficiency, photosensitive rash accompanied by neurological changes, reversible ataxia in siblings, and high excretion of indican or indolylactic acid. Pellagra is necessarily excluded by low or normal amino acid excretion.

Biochemical Lesion. The metabolic block is similar to that in phenylketonuria with indole compounds involved instead of phenylalanine, phenylacetic acid, and phenylacetyl glutamine. Hart (1956) considered the indole metabolites as a diversion

of tryptophan from a normal route of metabolism leading to nicotinic acid. A child with the H syndrome is thus unusually sensitive to nicotinic acid deficiency with consequent pellagra symptoms and psychosis or cerebellar defects and gait disorders related to other aspects of aminoaciduria. The resulting manifestations are due to a deficiency of tryptophan metabolites rather than to indole intoxication since the disease resembles pellagra. Excessive urinary excretion persists for more than 24 hours after tryptophan ingestion due to a defect in the transportation of both l- and d-tryptophan, affecting the proximal renal tubules, jejunum, and liver cells. Milne (1959) showed that only 1 per cent of ingested tryptophan appeared as kynurenine, compared with 3 to 7 per cent in the normal, accompanied by abnormal excretion of indolic acids. Indolelactic acid is the main derivative excreted after ingestion of l-tryptophan and indole-3-lactic acid after d-l-tryptophan.

Plasma amino acid levels are one third higher than normal. The amino acid pattern determined chromatographically is more significant than the total amino acid excretion, exceeding 10 times the normal concentration. The amino acid index or percentage of total urinary N contributed by α-amino acid N ranges from five to seven times the normal value. The aminoaciduria is renal in origin, the free amino acid comprising alanine, serine, threonine, asparagine, glutamine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine, citrulline. Jepson (1960) detected chromatographically additional amino acids moderately increased, i.e., taurine, glycine, cystine, asparatic acid, glutamic acid, leucine, methyl histidine, β-amino isobutyric acid. Dent (1954) found the renal clearance of total amino acid N elevated; Evered (1956), high clearances approximating normal GFR, indicating complete lack of resorption; Vaeon (1956), all other renal functions normal; Milne (1959), the amino acid resorption defect a phase of the deranged amino acid transport.

Indican is excreted in large but variable amounts in the urine, but sterilization with antibiotics prevents its formation. Oral administration of l-tryptophan enhances excessive excretion of indolylacetic acid and its conjugates, coupled with diminished conversion of kynurenine and nicotinamide. Indicanuria is marked, especially in indoxyl sulfate and bis-indolyl indoxyl, as final excretory products in the liver from intestinal indole absorption after the action of its microorganism or unabsorbed tryptophan. Horning (1958) found little excretion of 6-hydroxyskatole sulfate characteristic of the malabsorption syndrome; hence the responsible microorganisms differ in H disease. Rodnight (1955) attributed pellagra to diversion of tryptophan from its normal metabolic course into wasteful indican formation.

H disease is thus a disorder of amino acid transport into cells, particularly of the jejunum and the renal tubules, accounting for the slowed absorption of tryptophan, which favors abnormally large formation of indicans in the intestine after development of unusual intestinal flora and the constant aminoaciduria. The clinical manifestations are attributed to the deviations of tryptophan from its normal metabolic route leading to nicotinic acid. Treatment involves oral administration of nicotinamide, 40 to 150 mg./day, to alleviate the dermatitis and dementia and a high-protein diet to compensate for the high urinary loss of amino acids. But the sustained remission fails to suppress the aminoaciduria and urinary loss of indoles, although the condition improves with age. Holt[61] brought the disease under control

from the second week of life by means of a synthetic formula limiting the intake of the four key amino acids. The infant has remained free of the severe mental and neurological defects to date for a year, maintaining low blood levels of the branched amino acids except methionine. Southren et al[120] observed a similar syndrome in an adult, characterized by high blood serotonin levels, aggravated by reserpine administration, thus indicating functional deficiency of cerebral serotonin despite excessive serotonin production.

INBORN ERRORS IN CARBOHYDRATE METABOLISM

Galactosemia.

GALACTOSEMIC AMENTIA. Von Reuss (1901) described a marasmic infant with melituria who responded to a milk-free diet. Norman[105] and others observed normal infants at birth who gradually developed nutritional dystrophy, hepatomegaly, ascites, and edema on milk formula. All surviving infants remained malnourished, dwarfed, and mentally retarded, developing cataracts, cirrhosis of the liver, and neurological disturbances as long as milk and milk products were continued. The impaired ability to metabolize and utilize ingested galactose or galactose-containing compounds is transmitted by a single autosomal recessive gene and expressed as a characteristic cellular deficiency of galactose 1-phosphate uridyl transferase. The resultant accumulation in the tissue of galactose 1-phosphate leads clinically to nutritional failure, hepatosplenomegaly with cirrhosis, and mental retardation, and chemically to galactosuria, aminoaciduria, albuminuria, and impaired galactose tolerance test.

All manifestations regress or clear with early elimination of galactose from the diet. Anderson et al[2] showed that galactosemics retain about 3 per cent of the normal capacity to metabolize hexose, indispensable in brain lipid synthesis. Holzel (1957) established the diagnosis from a high level of galactose in the blood, 250 mg./100 ml. in comparison with the normal 70 mg., and an abnormal galactose tolerance test. Hsia et al[65] detected the heterozygous carrier of the abnormal gene by the 50 per cent decrease in galactose-1-phosphate uridyl transferase in the parents of affected children. Galactose is readily demonstrated in the urine by paper chromatography or the mucic acid test as long as milk-feeding is maintained.

A normal infant gradually becomes ill after milk ingestion with vomiting, diarrhea, and dehydration and consequent malnutrition from impaired utilization and jaundice from fatty infiltration and parenchymal involvement of the liver. Liver dysfunction, manifested by a rise in serum bilirubin, serum alkaline phosphatase, and prothrombin time, gradually returns to normal with elimination of milk or lactose-containing food but prolonged milk-feeding invariably produces irreversible liver injury, portal cirrhosis, and exitus. Once clinical manifestations extend beyond the second month there is lethargy and hypotonia, cataract formation and mental retardation. Foa et al[45] observed an accompanying hypoglycemia from insulin stimulation by hypergalactosemia; Komrower et al,[88] hypokalemia; Berger,[11] hyperchloremic acidosis. The mild case is considered a difficult feeding problem, remaining undiagnosed for months or years, vomiting milk mixtures, failing to thrive,

developing enlarged liver and spleen and eventually cataracts. The earliest clue is the finding of a reducing sugar in the urine identified as galactose.

Latent disease revealed by abnormal galactose tolerance is not diagnosed until late in childhood despite marked distaste for milk from birth. Darling et al[34] demonstrated albuminuria and aminoaciduria predominant in neutral aliphatic chain type, i.e., serine, alanine, glycine, threonine, glutamine, valine, and traces of phenylalanine, lysine, cystine, glutamic acid, methyl histidine, tyrosine, and aminoisobutyric acids, all of renal origin. Cusworth et al[32] showed that galactose or its metabolites interfere with amino acid resorption by the renal tubules, i.e., galactose-1-phosphate inhibits the renal tubular resorption of amino acids. Proteinuria, aminoaciduria, and galactosuria are all reversible phenomena resulting from renal disturbance.

Diagnostic tests include identification of the compound responsible for the melituria, galactose tolerance test, red blood cell assay for galactose-1-phosphate uridyl transferase, or red blood cell detection of galactose-1-phosphate excess. Commercial test preparations containing glucose oxidase, such as Ques-tape and Clinstix, give positive reactions in the presence of glucose. Bickel et al[12] preferred paper chromatography. Komrower et al[88] found the use of oral or intravenous galactose tolerance test hazardous in marked impairment of infant galactose utilization because of the danger of hypoglycemia and convulsions. Anderson et al[2] considered red blood cell assays of galactose-1-phosphate uridyl transferase sensitive and specific. Schwarz et al[118] developed in vitro tests based on red blood cell galactose-1-phosphate accumulation, but it requires two days to obtain a result.

Biochemical Lesion. Leloir[92] demonstrated the conversion of galactose to glucose-1-phosphate in four stages, each of which is catalyzed by a specific enzyme in the liver. Schwarz et al[117] found an abnormal red blood cell accumulation of galactose-1-phosphate in galactosemic children, hence a block occurring beyond galactose-1-phosphate, i.e., galactokinase is present in adequate amounts for the first reaction. Kalckar et al[75] showed that uridine diphosphogalactose-4-epimerase and uridine diphosphoglucose pyrophosphorylase are indispensable at the third and fourth stages and present in normal amounts in the red cells of galactosemic children, but galactose-1-phosphate uridyl transferase involved in the second stage is absent in galactosemic children. Isselbacher et al[66] confirmed the enzyme deficiency in galactosemic red blood cells but the presence of all other enzymes involved in galactose metabolism. Eisenberg et al[43] further demonstrated the same enzyme deficiency in the galactosemic liver. Apparently a specific gene controls the synthesis of galactose-1-phosphate uridyl transferase in the cells. Galactosemia is thus due to a metabolic block at the second stage, all other metabolic functions being normal.

Decreased galactose-1-phosphate uridyl transferase results in red blood cell accumulation of galactose-1-phosphate, responsible for galactose accumulation in the blood and tissues. This depresses blood glucose levels, induces convulsions and mental retardation, and causes cataract formation, cirrhosis of the liver, and renal disorders with aminoaciduria. The disturbances in the brain, lens, liver, and kidney are thus due to toxic effects of galactose metabolites especially on the inhibition of carbohydrate metabolism in body cells. Sidbury[119] demonstrated that galactose-1-

phosphate is a metabolic competitor for the normal phosphorylating regulating activity of phosphoglucomutase, the enzyme that controls conversion of glucose-1-phosphate to glucose-6-phosphate. Consequently, galactose-1-phosphate accumulation inhibits the normal cellular oxidative mechanism, diagnosed from galactose tolerance tests, excessive red blood cell galactose-1-phosphate, and galactosuria.

Chemical Therapy. The determining factor in neonatal well-being and survival in galactosemia is withdrawal of all milk, lactose, and galactose-containing foods. Successful therapy is a race against time. It will reverse possible intrauterine injury from maternal galactosemia and alleviate tissue damage manifest in the brain, lens, liver, and kidney. Cox et al[27] observed improvement after weaning from breast- to bottle-feeding with its lower lactose content. Hobiel (1952) prescribed a milk-free diet consisting of egg, rice, flour, sugar, and margarine supplemented by orange juice, vitamins, and calcium gluconate. Nutramigen and Mull-soy each contain about 1 per cent galactose, insufficient to injure the galactosemic child. Semisolid and solid foods are gradually added to the formula for three years in the form of fresh or cooked fruit; vegetables, except peas; meats, except brains; unprocessed fish; cheddar but not cream cheese; bread made from cracked wheat or Vienna bread. But canned prepared cereals, vegetables, and meats must be avoided because they contain milk, whey, buttermilk solids, or nonfat dry milk. Calcium supplements are essential unless adequate amounts of the formula are offered daily to older infants and children.

Adequate dietary control in the early months of life is a direct function of the intelligence level finally attained. But the galactosemic gradually develops tolerance for galactose without ill effects. Komrower et al[88] demonstrated improvement in galactose utilization and diminishing galactose:body weight ratio with increasing age. Isselbacher et al[67] observed untreated galactosemics escape mental deficiency because of the development of U D P G galactose pyrophosphorylase, which serves as an accessory pathway to galactose metabolism. Platt[108] contended that infants have sufficient galactose for cerebroside synthesis as borne out by long-range studies of milk allergy showing no evidence of increased susceptibility to CNS demyelinating disorders. Actually the galactosemic has the enzyme uridine diphosphate galactose-4-epimerase, which enables endogenous synthesis of galactose from glucose and galactolipid formation in CNS and other tissues without dietary galactose.

Hypoglycemia Syndromes.

Idiopathic Hypoglycemia. Heredofamilial hypoglycemic attacks of limpness, nervousness, irritability, pallor, cold sweats, flushing, coma, and convulsions occur in boys about twice as frequently as in girls. If the symptoms simulating hyperinsulinism are not properly diagnosed or treated, the consequence is mental retardation and physical deterioration. The fasting blood sugar is depressed below 40 mg./100 ml. The electroencephalogram shows high voltage slowing at a rate of 2/sec. during attacks with well-formed spikes between the slow waves. Differential diagnosis involves epilepsy, adrenal cortical insufficiency, pituitary insufficiency, hepatic disease, glycogen storage disease, galactosemia, and cretinism. Treatment with adrenocorticotropin, 4 mg./Kg./day in divided doses, is continued for several days until the condition is controlled and the dosage reduced to 1 mg./Kg. body weight

per day in divided doses as Acthar gel. The individualized dosage is established by fasting blood sugar determinations and the amount gradually reduced to zero over a period of a year when a normal glycemia is maintained.

Idiopathic hypoglycemia may arise spontaneously in infants, and acquired hypoglycemia as a result of drug therapy, an islet tumor in the pancreas, hepatic disease, lesions of the brain stem and hypothalamus. All types of hypoglycemia reveal manifestations of anoxia, but hypoglycemia is not anoxia in the strict sense. Oxygen is available as indicated by analysis of the arterial and venous oxygen tension, but the arteriovenous gradient is reduced for oxygen is not used up by the nervous parenchyma because of glucose diminution. Himwich et al[59] emphasized the similarity between severe hypoglycemia and anoxia.

Labile cerebral phosphate falls and inorganic phosphate rises as in hypoxia. Glucose and glycogen are markedly reduced, but unaltered in hypoxia. Lactic acid may be decreased in hypoglycemia and increased in anoxia. McIllwain[96, 97] observed the compensatory increase in blood flow and vasodilatation to be less marked in hypoglycemia than in anoxia. Lawrence et al[91] found coma of one to three hours' duration associated with complete recovery. It is not known, however, whether irreversibility of coma coincides with irreversible histological damage to the nerve cells. There is evidence that biochemical irreversibility precedes histological degeneration by some time, thus accounting for some incongruity between the signs of deep coma and the severity of the histological change.

Leucine Sensitivity Hypoglycemia. Cochran (1956) observed three members of one family who developed hypoglycemia with pallor, sweating, and convulsions after a large meal, despite normal electroencephalogram. Glucose, insulin, and epinephrine tolerance tests were normal but ACTH and cortisone failed to alter the blood sugar levels. Administration of casein, leucine, and isovaleric acid depressed the blood sugar to half the fasting levels within 30 minutes due to an increased effect of circulating insulin on intracellular carbohydrate metabolism or to an increased secretion of insulin by the islets of Langerhans. Hypoglycemia due to leucine sensitivity may be diagnosed by a test feeding of casein, 1.5 Gm./Kg., and leucine, 0.15 Gm./Kg., to the fasting patient and determining the blood sugar levels at frequent intervals for 90 minutes. Treatment of susceptible individuals involves a low-protein diet.

INBORN ERRORS IN LIPID METABOLISM

Neurolipidoses. Lipidoses of the developing brain are heterogeneous neuronal storage diseases of abnormal lipid metabolism with the common characteristic of excessive lipid accumulating in cells of mesenchymal origin, e.g., ganglioside in the Tay-Sachs disease, kerasin in Gaucher's disease, cholesterol and its esters in Schüller-Christian disease and xanthomatoses, sphingomyelin in Niemann-Pick disease. The lipids accumulate as mixtures varying in proportions not only from organ to organ but from family to family. Clinical manifestations appear in Gaucher's and Niemann-Pick disease after the lipid changes in the cells are well developed, but a granuloma appears first in Schüller-Christian disease and cholesterolization second-

arily with the progression of the disease. All neurolipidoses involve disturbances in sphingolipid metabolism in nerve sheaths during myelination. Sphingolipids accumulate in the white matter of the brain and spinal cord forming half the total lipids. The abnormal lipids accumulate in the nerve cells causing distention of the cyton and displacement of the nucleus and neurofibrils. Sobotka (1942) attributed lipidoses to absence of specific esterases, and Thannhauser et al,[124] to absence of coenzymes. Reticuloendothelial components share with similar tissues throughout the body in the pathological deposition of lipids in these diseases and are likewise altered in the nonlipid Letterer-Siwe's disease.

Cumings[30, 31] diagnosed cerebral lipidoses from chemical examination of a small portion of cerebral tissue obtained by operation during life, since the chemical composition is markedly altered by formalin fixation or from brain tissue obtained post mortem. The water content of preserved material is always less than that of fresh biopsy tissue by about 3.8 per cent for white matter and 3.4 per cent for the cortex after formalin fixation. Total phospholipid, sphingomyelin, cephalin, and lecithin are considerably diminished. Amaurotic family idiocy reveals increased gangliosides with marked loss of gangliolipids in the cortex; metachromatic leukodystrophy, increased hexosamine, and decreased phospholipids in the white matter; multiple sclerosis and sudanophilic diffuse sclerosis, loss of phospholipids but presence of esterified cholesterol in active lesions; tuberous sclerosis, only slight chemical alterations from the normal, but diagnostic on naked eye examination; subacute encephalitis of inclusion body type, decreased phospholipids, and increased hexosamine in both white matter and cortex. Few adolescents survive the destructive effects of lipid infiltration in any of the neurolipidoses.

INBORN ERRORS IN METAL METABOLISM

Hepatolenticular Degeneration.

Ceruloplasmin Deficiency. Wilson[138] described a heredofamilial disorder in young people characterized by cirrhosis of the liver and degenerative changes in the brain, especially in the basal ganglia. The greenish brown Kayser-Fleischer corneal ring is pathognomonic. Later, Wilson[139] demonstrated disorganization of the lenticular region of the brain, golden-brown pigmentation in the cornea, multilobar cirrhosis of the liver, and hemorrhage from esophageal varices. The primary defect is in Cu rather than protein metabolism with decreased or abnormal ceruloplasmin synthesis and positive Cu balance. Plasma Cu is transported as a direct-reacting fraction bound to albumin and an indirect-reacting fraction corresponding to ceruloplasmin. Ceruloplasmin deficiency decreases the indirect-reacting Cu fraction with consequent increase in Cu absorption by the digestive tract and increase in the direct-reacting Cu in plasma.

Ceruloplasmin probably controls Cu absorption from the gastrointestinal tract; hence its deficiency accounts for increased Cu absorption. Melander et al[100] also found ceruloplasmin to maintain the integrity of the blood-brain barrier. Excess Cu is deposited in the tissues causing lenticular degeneration of the brain, Kayser-Fleischer rings in the cornea, and cirrhosis of the liver, or is chelated with amino acid and excreted in the urine. Normally intravenous Cu^{64} produces a rapid fall in

serum radioactivity followed by a secondary rise, but in Wilson's disease, Bearn (1960) observed a slight fall initially and no secondary rise since the latter is normally due to Cu^{64} incorporation into ceruloplasmin. Scheinberg et al (1952) detected plasma ceruloplasmin decreased to 25 per cent of the normal level, a deficit present from infancy that usually precedes clinical signs of the disease. The late onset of disease is due to the gradual increase in body Cu over a period of years. Defective synthesis of the plasma ceruloplasmin decreases serum Cu and increases albumin-bound Cu and urinary Cu excretion.

Wilson's disease is transmitted as an autosomal recessive, predominant in consanguinity. Gitlin[47] considered deficient ceruloplasmin synthesis as an expression of an allele leading to synthesis of an altered apoceruloplasmin that cannot bind Cu, or as a homozygous form of a modifying gene controlling ceruloplasmin synthesis in the heterozygote. Silverberg (1958) observed suggestive diminutions in serum ceruloplasmin levels among the relatives, whom Sass-Kortsak et al[113] found able to incorporate Cu^{64} into ceruloplasmin in contrast to true cases that fail to do so. Apparently, a decreased rate of Cu incorporation into ceruloplasmin is more clearly related to the basic defect than the change in rate of synthesis of ceruloplasmin judged from its blood levels. Administration of Cu^{64} thus increases the number of heterozygotes detectable with demonstrable ceruloplasmin abnormalities. But decreased serum Cu and ceruloplasmin are occasionally found in apparently normal heterozygotes.

The varied manifestations preclude presentation of a typical clinical picture. Adolescence heralds the onset of bulbar symptoms while hepatic cirrhosis remains silent. The acute progressive spastic rigidity of the face, mouth, and pharynx causes dysarthria and dysphagia, preceded by a brown ring at the limbus of the cornea. Parkinsonian facies develops gradually accompanied by spells of weeping and laughter, loss of emotional control, muscular rigidity, and the cogwheel phenomenon. The acute form is manifested by an unrecognized liver disorder and abdominal disturbance accompanied by irregular fever, jaundice, and toxicity, and the chronic form, by tremor, stiffness, and hypertonia. Less often, the condition is heralded by esophageal hemorrhage from cirrhosis of the liver without neurological signs, but the presence of corneal pigmentation establishes the diagnosis. Chalmers et al[24] observed neurological manifestations alone and liver disease alone, although both tend to occur simultaneously. Febrile attacks, hepatic coma, schizophrenic behavior, jacksonian epilepsy, hemiplegia, and hepatic coma may mask the underlying disease or usher in the terminal stages.

The blood shows hypochromic microcytic anemia accompanied by splenomegaly, leukopenia, and thrombocytopenia; CSF, increased number of cells and protein; liver profile, the degree of hepatic derangement; radiograms, osteoarthritis, bone fragmentation, and, rarely, osteomalacia and spontaneous fractures. Necroscopy reveals widespread CNS changes, rings of periocorneal pigmentation, and cirrhosis of the liver. The brain shows extensive degeneration, cavitation of the lenticular nucleus, and Alzheimer's giant cells. Cu deposition in the kidneys gives rise to disturbed tubular glycosuria, aminoaciduria, and phosphaturia.

Biochemical Lesion. Ceruloplasmin was isolated by Holmberg et al[60] from human

blood as the specific sky-blue Cu oxidase of mol. wt. 151,000. Its 8 Cu atoms per molecule bind 95 per cent of total serum Cu to α_2-globulin and the remaining 5 per cent Cu is loosely attached to serum albumin for transport. Watson (1949), however, showed that some Cu normally present in human serum is bound by β-globulin. Cumings (1957) correlated oxidase activity with the Cu level of the β-globulin complex rather than with that of the α-globulin or γ-globulin complexes. The normal infant shows low ceruloplasmin levels owing to immaturity of the synthetic mechanisms, but the older child gradually develops the normal range of 16 to 33 mg./100 ml. Plasma Cu distribution represents 25 per cent attached to α-globulin, 50 per cent to β-globulin, 20 per cent to γ-globulin, and 5 per cent to albumin. Ceruloplasmin is undetectable in the plasma while the normal level is about 15 mg./100 ml. Scheinberg et al (1952) found 9.4 mg./100 ml. by the ascorbic acid method in comparison with the normal 32 mg., the lower ceruloplasmin values being due to hemoglobin interference. Spectrophotometric methods yield ceruloplasmin levels comparable to the immunochemical method.

Normally, Cu is taken up from the intestine loosely bound to albumin for 24 hours and transferred to globulin for firmer binding, but in Wilson's disease the primary defect is failure to bind Cu absorbed from the intestines to serum globulins. Zimdahl et al[144] demonstrated increased Cu absorption from the intestinal tract; Mathews et al,[99] less Cu^{64} in the stools of patients than in controls, while the urine contained more Cu^{64} than in the normal subjects; and Cartwright et al,[23] a positive Cu balance. Bearn[8] attributed ceruloplasmin synthesis to failure to transfer absorbed Cu^{64} from plasma albumin to the plasma α_2-globulin carrier. Most of the absorbed Cu^{64} remains labile, adsorbed by albumin, and therefore free to combine with the proteins of the brain, liver, and other tissues or to be excreted in the urine chelated by amino acids and peptides.

Marked Cu retention by vital tissues maintains despite excessive urinary Cu excretion associated with low blood Cu and ceruloplasmin levels. Cumings (1954) found 5 to 10 times as much Cu in the brain and 5 to 20 times as much in the liver and kidney as in the normal tissues. Wintrobe et al[140] showed that Cu deposited in the brain and liver produces characteristic lesions; Denny-Brown (1954), that Cu bound to the cornea gives the typical granules; Uzman et al,[135] that the pigmented Cu granules in the Kayser-Fleischer ring form two layers of colloidal Liesegang rings responsible for the diverse colors; Stein et al,[121] that Cu accumulation in the kidney destroys enzyme systems, which impair resorption of amino acids and peptides and cause increased excretion. Cumings[30, 31] demonstrated plasma Cu half bound to the globulins and half loosely to albumin from which Cu is readily taken up by brain and visceral proteins and excreted by the kidney. Consequently, Glazebrook[48] found 300 μg. Cu per 100 ml. in blood; Cartwright et al,[23] 20 μg./100 ml. Cu in cerebrospinal fluid. Wintrobe et al[140] observed that patients absorbed more Cu from food in the intestinal tract than normal individuals but the normal Cu transference from albumin to globulin in blood is abolished owing to failure of ceruloplasmin synthesis. Cartwright et al[23] confirmed markedly decreased ceruloplasmin accompanied by absence of oxidase activity and rise in albumin-bound copper.

Defective ceruloplasmin synthesis was attributed by Uzman et al[134] to faulty pro-

tein metabolism since liver proteins bind more readily with Cu than normal liver proteins, a mechanism that Porter (1957) found applicable to brain proteins. An abnormal peak in the electrophoretic pattern obtained from the diseases liver extracts indicated unusually high Cu-binding. Consequently Hall (1957) hypothesized faulty genetic control of a specific protein molecule involving Cu and ceruloplasmin. Scheinberg et al[115] observed a diminished half-life of ceruloplasmin in hepatolenticular disease of 3.4 to 4.7 days compared to the normal 110 to 170 owing to diminished rate of synthesis. Ceruloplasmin Cu can be released from the protein; hence there is a gradient at the level of the intestinal mucosa necessary and sufficient for more Cu to be resorbed into the circulation than normal. Apparently, the affected individual is born with a deficiency or absence of ceruloplasmin and absorbs more Cu than normal with gradual development of the disease as tissue damage increases. This does not explain the high tissue Cu uptake, which leads to their destruction, while excessive Cu feeding does not produce such lesions. Uriel et al[129] demonstrated electrophoretically that ceruloplasmin of the normal individual is the same as that in the affected individual; hence faulty synthesis is the underlying cause.

Urinary copper is greatly increased in advanced stages of the disease. Earl et al[41] reported values exceeding 500 μg./day in comparison with the normal 10 to 100 μg. Eckhardt et al[42] identified histidine, lysine, and thrionine; Dent (1954), cystine and lysine; Blaha (1954), increased glycine, cystine, glutamic acid, and proline; Uzman et al,[130] increased aminoaciduria, low serum inorganic potassium, and failure of normal tubular transport of phosphate, which is partly responsible for osteomalacia; Litin et al,[94] hypercalciuria. There is marked reduction in renal plasma flow, decreased GRF, and impaired urine-concentrating ability, paralleling the duration and severity of the disease. The tubular resorptive mechanism is impaired resulting in excessive aminoaciduria, since serum amino acid levels are normal. There is also an increased excretion of amino acids as conjugated linkages by which the free acids are liberated by acid hydrolysis. Uzman et al[132] considered excretion of specific oligopeptidase as a cardinal abnormality, probably formed by an abnormal proteolytic enzyme in the tissues causing intracellular accumulation of oligopeptide.

Aminoaciduria develops because peptides compete with amino acids for resorption and the Cu-peptide complex is absorbed preferentially. Bishop et al[15] considered low serum uric acid associated with increased urinary uric acid excretion, pathognomonic of Wilson's disease; Stein et al,[121] gross aminoaciduria, especially threonine, cystine, proline, and citralline, comprising amino acids in both free and conjugated form, 300 to 800 mg./day, without any noticeable effect on the nutritional state. The urinary loss is 2.5 times normal, yet the amino acid content of plasma remains unaltered qualitatively or quantitatively. Bearn[10] attributed the aminoaciduria to inefficient resorption of amino acids by defective renal tubules from the glomerular filtrate, accompanied by renal glycosuria, phosphaturia, and uricosuria, as well as the progressive deterioration in renal function due to Cu deposition in sites causing interference with the enzyme responsible for the transport of materials across epithelial membranes.

Chemical Therapy. Cu accumulation in the tissue is prevented and eliminated by diminishing intestinal absorption and increasing urinary Cu excretion. Thera-

peutic decrease in tissue Cu stores tends to alleviate the symptoms of Wilson's disease, but it is difficult to reduce Cu below 1.0 mg./day without considerable caloric restriction unless ingested carboresins and KS reduce Cu absorption. Zimdahl et al[144] advocated KS, 10 to 20 mg. three times daily orally, to increase Cu precipitation from food in the intestinal tract and thus decrease absorption. Cumings (1951) administered 2.5 mg./Kg. dimercaptopropanol or BAL intramuscularly, twice daily for five days, repeated at 10-day intervals every six weeks to six months. Porter[109] observed reduction in the tremor, improvement in speech and handwriting, and increase in urinary Cu excretion without any alteration in aminoaciduria. Bearn[9] found it effective only in the absence of gross destructive lesion in the basal ganglia. Children respond poorly but adolescents with the pseudosclerotic variety progress favorably on continuous BAL therapy.

Penicillamine, 1 Gm./day orally, introduced by Walshe (1956), increases urinary Cu excretion. Zimdahl et al[144] administered polysterene sulfate resin orally; Hall (1957), sodium-calciumedetate. Adolescents with severe lenticular degeneration and destructive brain lesions fail to respond. Versene or dicalcium disodium versinate, another chelating agent, requires intravenous administration to increase urinary copper excretion less effectively. Unfortunately, patients become resistant to each of these cupruric agents. Bearn[8] offered a high-protein diet and Mathews et al[98] injected amino acids intravenously to increase urinary Cu excretion. Bickel et al[14] increased serum ceruloplasmin by continuous infusion replacement, and Bearn,[10] by estrogen stimulation, without clinical improvement. The diet should exclude Cu-containing foods, such as liver, spinach, chocolate, and nuts, and delimit the intake to less than 1.5 mg./day.

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Study of an Experimental Syndrome of Excitation-Hypotonia

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The study conducted on convulsions caused by oxygen under pressure greater than one atmosphere led to the pharmacological study of several antioxidants.[4, 5] It was found that some of these antioxidants could achieve a true metabolic resuscitation after severe anoxia.[6]

We were able to demonstrate experimentally in animals the particular neuromuscular syndrome that many of these antioxidants cause, and it is only this aspect that we shall consider here. We have attempted to dissociate the elements and to reveal the existing relationship between the chemical structure and the neuromuscular excitation and hypotonia phenomena.

THE EXCITATION-HYPOTONIA SYNDROME

The excitation-hypotonia syndrome appears in two to six minutes with doses that vary according to the agent studied, but that are always high. The syndrome is characterized by general tremulation and incoordinated muscle twitching. The animal is spread out on the table with the hindlegs in extension. Except with very high doses, which are generally lethal, neither convulsions, rigidity, nor loss of consciousness is observed. The normal condition returns within 20 to 40 minutes, depending on the dose employed, and the return is sudden and without sequelae. An identical syndrome can again be obtained with an additional injection. The syndrome can be induced in the rat, rabbit, and dog by intraperitoneal or intravenous injections and, in sufficiently large doses, also by oral administration.

In view of the large doses required, we consider this a physiopathological test and not a test of the activity of the substances studied. But our studies did permit us to define certain relationships between the chemical structure and the pharmacological activity.

Substances Studied. We first injected substances that are considered to possess antioxidant properties because of the presence in their formula of one or more labile hydrogen atoms and that are, therefore, able to yield odd electron structures. (We shall use the following conventional abbreviations: L.D.L. = lower dose limit; L.D. = lethal dose; D = duration of neuromuscular activity. In this case, the first number relates to the L.D.L. and the second to the L.D.). The results are valid for rats of the Wistar breed, Commentry branch, of 120 to 350 Gm. injected intraperitoneally.

THE DIPHENOLS.

Para derivatives: Hydroquinone: L.D.L.: 50 mg./Kg. L.D. : 200 mg./Kg. D. : 20′–20′

Ortho derivatives: Pyrocatechol: L.D.L.: 50 mg./Kg. L.D. : 100 mg./Kg. D. : 20′–20′

Meta derivatives: Resorcinol: L.D.L.: 50 mg./Kg. L.D. : 200 mg./Kg. D. : 25′–25′

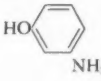
THE DIAMINES.

Ortho derivatives: o-Phenylenediamine: L.D.L.: 2 Gm./Kg. L.D. : 2.50 Gm./Kg. D. : 90′

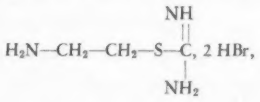
Para derivatives: p-Phenylenediamine: L.D.L.: 50 mg./Kg. L.D. : 100 mg./Kg. D. : 90′

THE AMINOPHENOLS.

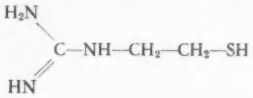
Ortho derivatives: o-Aminophenol: L.D.L.: 300 mg./Kg. L.D. : 300 mg./Kg. D. : 100′

Meta derivatives: m-Aminophenol:  L.D.L.: 75 mg./Kg. L.D. : 1 Gm./Kg. D. : 15′–360′

SULFUR-CONTAINING COMPOUNDS. 2-Aminoethylthiouronium hydrobromide



which would give in neutral solution a sulfydryl compound with the following structure:

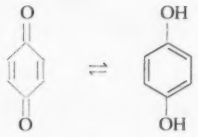


L.D.L.: 125 mg./Kg.
L.D. : 400 mg./Kg.
D. : 10′–5′

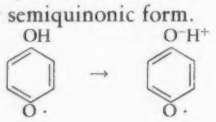
We have conducted a detailed pharmacological study of some of these substances.[5] All of them cause an identical excitation-hypotonia syndrome with the L.D.L.

PARAQUINONE AND QUINHYDRONE. With paraquinone (the diketone structure corresponding to the diphenol), the hypotonia syndrome is predominant. The slight excitation, however, is always transitory with average doses, and more

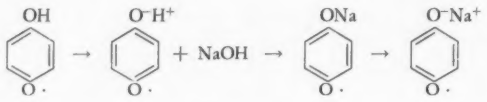
important with higher doses. Paraquinone in solution is in equilibrium with hydroquinone.



With quinhydrone (the hydrogen of which is always acidic, as in phenol), the excitation syndrome is practically nil; the inhibition syndrome is very important. Now, quinhydrone has a purely semiquinonic form.



Formation of the sodium salt causes the disappearance of all neuromuscular action.



PHENOL AND ANILINE. THE NAPHTOLS. We had already observed the marked and rapid effectiveness of phenol:

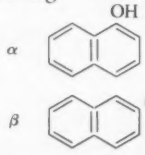
L.D.L.: 50 mg./Kg.
L.D. : 350 mg./Kg.
D. : 15′–120′

and of aniline:

L.D.L.: 1/32 ml.
L.D. : 1/32 ml.

which cause a strong and rapidly appearing (one-minute) excitation-hypotonia syndrome. Although these two compounds are usually considered as possessing antioxidant properties, however, they seem incapable of producing odd electron structures. Indeed, when their hydroxyl group loses one hydrogen, it is an acid one, a proton (H^+).

We then studied the action of the naphtols in which the phenol nucleus is bound to a second benzene ring. We have tested the α and β naphtols.

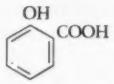


α L.D.L.: 100 mg./Kg.
L.D. : 100 mg./Kg.

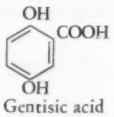
β L.D.L.: 100 mg./Kg.
L.D. : 500 mg./Kg.

These agents were found to be much more inhibiting than phenol, especially so in the case of β naphtol. The addition of the second benzene ring increases the inhibiting aspect at the cost of the stimulating properties of the phenol.

Introduction of a Carboxyl Group into the Benzene Ring. We were able to demonstrate that salicylic acid and gentisic acid do not induce the excitation-hypotonia syndrome.



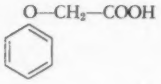
Salicylic acid



Gentisic acid

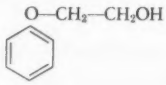
Formation of Phenol Ethers.

With an Acid Alcohol. Formation of an ether also suppresses the appearance of the excitation-hypotonia syndrome. Thus, phenoxyacetic acid does not produce any action:



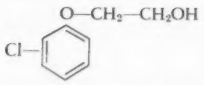
With a Glycol. We have studied a known antioxidant: phenoxetol and its derivatives:

Phenoxetol:



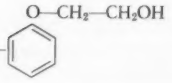
L.D.L.: 325 mg./Kg.
L.D. : 575 mg./Kg.
D. : 30′–60′

Chlorophenoxetol:



L.D.L.: 300 mg./Kg.
L.D. : 400 mg./Kg.

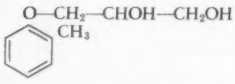
Propylenephenoxetol:



L.D.L.: 200 mg./Kg.
L.D. : 350 mg./Kg.

These compounds cause only a considerable hypotonia with a major drop in temperature, but without stimulation.

It is of interest to relate this neuromuscular inhibition with that obtained with cresoxypropanediol, which has a similar structure.



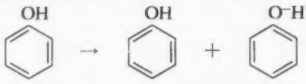
Let us also remember that a compound that has recently been introduced in anesthesia, G.29, contains the phenolic function of eugenol blocked by an acid alcohol. To this should be added that the alcohol group frequently acts as an antioxidant.

An identical syndrome was produced with propylene glycol, ethyl-, and secondary octyl-alcohol, and it is a well-known fact that a number of amino-ethers of phenols and alcohols possess a centrally potentiating action on general anesthetics. Buchel and Levy[2] have recently made an extensive study of this problem.

Relationships Between Structure and Pharmacological Activity. First we wanted to define the mechanism of action of phenol in the production of the excitation-

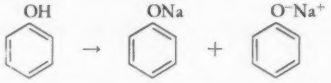
hypotonia syndrome since it is understood that at first sight this compound cannot give rise to an odd electron structure.

The ionization of phenol in water leads to the following simultaneous structures:

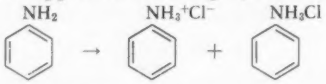


Addition of sodium hydroxide to the solution until about *p*H 8 yields:

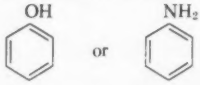
The excitation-hypotonia syndrome persists after the injection of this solution, but the addition to the phenol of a large excess of sodium hydroxide to *p*H 13 to 14 yields:



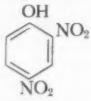
The syndrome does not appear after the injection of this solution. The same phenomenon is again seen with aniline, which is alkaline and the excitation-hypotonic effect of which is suppressed in strong hydrochloric acid medium.



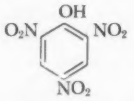
The appearance of the excitation-hypotonia syndrome can only be associated with the phenol or NH_2 group, or better still with the whole molecule:



The nitration of the benzene ring, as found in dinitrophenol and in picric acid, causes a more pronounced ionization of the OH:



Dinitrophenol



Picric acid

We observed that these two compounds do not cause an excitation-hypotonia syndrome.

The excitation phenomenon must, therefore, be due to the benzene nucleus provided it is substituted only by either an OH or an NH_2 group.

PHARMACOLOGICAL INHIBITION TESTS OF THE EXCITATION-HYPOTONIA SYNDROME

We injected intraperitoneally in the rat a number of drugs in an attempt to suppress the excitation-hypotonia syndrome.

Chlorpromazine, 2 mg./Kg., has no effect. With 5 mg./Kg. the appearance of

tremulations is greatly delayed (20 minutes after the injection of 100 mg. of hydroquinone instead of 2 minutes).

Pentothal in anesthetic doses does not suppress the tremulations and seems even to intensify them.

90° Ethyl Alcohol, 4 ml./Kg., suppresses the appearance of tremulations, as does ethyl ether in anesthetic doses.

Atropine, 0.5 mg./100 Gm., can achieve the suppression of tremulations only when combined with thiopental. The same is seen with diethazine, 800 mg./Kg.

TENTATIVE DETERMINATION OF THE NEUROPHYSIOLOGICAL SITE OF ACTION

It was interesting to examine whether suppression of the physiological function of certain structures modified the syndrome. We have tested in the rabbit the effects of: upper medullar section, curare, and the drug on the tibialis muscle after sciatic section following direct intra-arterial injection with or without preinjection of the synthetic curare.

Technique (in the Rabbit). Using general anesthesia with intravenous pentobarbital we performed tracheotomy and controlled ventilation with + and − pressures, as well as laminectomy of the first cervical vertebrae and opening of the dura mater. Intravenous injection of 50 mg./Kg. of hydroquinone was given. Tremulations appeared.

The same protocol was reproduced when hydroquinone was injected after medullar section.

Curare Alone. Pentobarbital anesthesia was given, with intubation, controlled ventilation, and intravenous injection of hydroquinone, 50 mg./Kg. Tremulations appeared.

Intravenous injection of synthetic curare, 10 mg./Kg., was given.

Myographic Study of Anterior Tibialis Muscle. Intravenous pentobarbital anesthesia was given, with intubation, and controlled ventilation. Section of the femoral nerve and of the sciatic nerve and its branches after procaine hydrochloride infiltration was performed. Isolation of the terminal tendon of the anterior tibialis, which was connected to a myograph, was performed.

Intraperitoneal injection of hydroquinone (50 mg. and then 150 mg.) was given before and after systemic curarization (10 mg./Kg.).

Results. High medullar section had no effect on the excitation syndrome. Curare alone caused inhibition of the excitation syndrome. Myographic study of the tibialis revealed that hydroquinone injected by the intra-arterial route causes a sudden contraction of the muscle.

After systemic curarization (intravenously), the same injection has no effect on the muscle.

DISCUSSION

Many of the compounds that we have studied are considered to possess antioxidant properties. But the fact that not all of them can give rise to a free radical would seem to indicate that the excitation-hypotonia syndrome does not depend

on the presence in the structure of an odd electron or of a labile hydrogen atom. In our view, the excitation-hypotonia syndrome must be regarded as a secondary phenomenon related to the presence of an OH or NH_2 group.

These observations do not lessen the possibility of a "metabolic resuscitation" related to odd electron structures, a hypothesis confirmed by our animal experimentations as well as by early clinical results.

Is It Possible to Find the Metabolic Substratum of the Excitation-Hypotonia Syndrome? Tarakhovskii[7] has demonstrated that ganglioplegic action could be antagonized by cysteine, reduced glutathione, or urea. The two former compounds are antioxidants, although with only a low potential and possess a labile hydrogen atom. On the other hand, urea frees the reactive sulfhydryl groups of proteins. Independently of this, we have also noted that 2-amino-ethylisothiouronium, which frees SH groups, antagonizes the action of the ganglioplegics on blood pressure.[5]

Vasodilation, bradycardia, eventual salivation, antagonistic action on the intestinal muscles, myosis, facilitation of hypothermia, decrease in the oxygen consumption of small animals, the potentiation of atropine-induced hypertension (nicotinic stimulating effect), the antithyroid action that we have noted clinically[5, 6] —all seem to indicate that a compound such as 2-amino-ethylisothiouronium facilitates the cellular synthesis of acetylcholine, particularly since it has no anticholinesterase activity.

With large doses, however, it can cause an excitation-hypotonia syndrome.

The activity of quinones is more complex. The importance that is now attributed to coenzyme Q in the course of the coupling processes between phosphorylations and oxidations with the production of a semiquinonic form is now known. Brodie and Pallantine[1] have just demonstrated that vitamin K_1 is able to re-establish phosphorylations in bacterial systems inhibited by uncoupling agents. But these authors have noted that quinone (1-4 benzoquinone) is unable to do so.

In any event, the necessity for acetylcholine synthesis of this coupling between phosphorylations and oxidations is known.

Some strongly uncoupling compounds, such as dinitrophenol, do not cause an excitation-hypotonia syndrome. But at present it is impossible to define the relationships between the latter and the idea of coupling and uncoupling. Two concepts, however, are thought stimulating. These are: the structural simplicity of the compounds studied, and the monotony, intensity, and purity of the observed syndrome, which would indicate that these aspects are due to an essential metabolic phenomenon of the type that couples phosphorylations and oxidations.

Can We Consider a Neuronic Mechanism in the Excitation-Hypotonia Syndrome? The interpretation of such a mechanism is also complex. The myographic study and the suppression by curare of the contracting effect of the intra-arterially injected drug leads one to consider an action on the motor end plate. On the other hand, it is tempting to assume that the excitation syndrome depends on a metabolic acceleration leading to a stimulation of the synaptic functions. The possibilities of resuscitation after electroshock or after cerebral anoxia also lead one to consider an accelerated neuronal repolarization.

The same doubt remains concerning the neurophysiological mechanism. The

fact that the high medullar section does not hinder the appearance of the syndrome shows at least that the participation of the cerebral centers is not predominant. These facts are confirmed by the inability of pentobarbital to control tremulations. It is more difficult to interpret the action of diethazine and of atropine, which are known to act on the extrapyramidal track and which, when combined with pentobarbital, inhibit tremulations.

The excitation-hypotonia syndrome probably finds, then, its origin at the level of the medullary motoneurons. But what is the mechanism? The whole syndrome may be explained by a generalized activity of the drugs on all the medullary neurons rather than through a selective action on the fine fiber structures of the γ system or on certain stimulating neurons. It is, in fact, known that the neurons most sensitive to pharmacological action seem to be the cells of Renshaw.[3] These form a feedback circuit, particularly on the α tonic neurons, whereas the phasic motoneurons seem deprived of such a circuit.

Therefore, it can be conceived that general metabolic excitation of the medullary neurons may be at the origin of the excitation-hypotonia syndrome. The decrease in tone may be the consequence of a stimulation of the Renshaw cells, but the stimulation of the phasic motoneurons would be the cause of the tremulations and of the incoordinated contractions.

It appears even more clearly that the feedback circuits of the type produced by the Renshaw cells are an aspect of the functional structure of all levels of the cerebrospinal axis. If we admit a pharmacological action on this type of cell, it is probable that this action is also exerted at cortical and subcortical levels.

The aim of this work is not to solve all the problems, which have barely been raised, but simply to describe some experimental observations and to consider certain mechanisms that control these phenomena at their various physiological levels.

SUMMARY

The authors have studied a neuromuscular syndrome that combines excitation (tremulations) and hypotonia caused in the animal by the injection of various chemical agents, many of which possess antioxidant properties. They reach the following conclusions: Excitation phenomena are associated with the benzene nucleus provided that the latter possess no other substituent than an OH or NH_2, and hypotonia phenomena are associated with the poorly ionizable hydroxyl OH attached to an aliphatic chain.

The observed facts cannot be unquestionably related to the phenomena of coupling between phosphorylations and oxidations nor to an action on neuronal polarization. The excitation of the metabolic processes, particularly sensitive on the feedback circuit of the Renshaw type, would, however, yield a coherent interpretation.

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OINTMENT CAUSES DEPIGMENTATION OF SKIN. Daily application for two years of the ointment monobenzil ether of hydroquinone changed the skin of 16 Negroes to white, according to Robert Stolar (Georgetown University School of Medicine). The patients were all suffering from vitiligo, causing sections of the skin to fade and blotch. Stolar also reports that methoxypsoralen has been used by him to darken the skin of some patients.

COMPOUND FOR TREATMENT OF CHRONIC DERMATITIS. A compound that converts hexavalent chromium, pin-pointed as the exacerbating agent in chronic dermatitis, into the relatively harmless trivalent state was described at the meeting of the American Academy of Dermatology and Syphilology. Sodium pyrosulfite was used as a reducing agent and tartaric acid as the chelating agent, in combination with glucose and ammonium chloride. Patch tests with a 10 per cent concentration of the compound showed that it prevents allergic reaction and is nonirritating to the skin.

HYPOGLYCEMIA THERAPY. Glucagon, a pancreatic hormone, can be administered intramuscularly or subcutaneously to treat hypoglycemic reactions in diabetic patients and to terminate insulin coma in psychiatric patients. Recovery usually occurs in from 5 to 20 minutes. The agent is marketed by Lilly.

ACUTE BARBITURATE INTOXICATION. Forced diuresis, combined with standard measures, was used in treatment of 605 cases of acute barbiturate intoxication, according to a report to the Swedish Society of Internal Medicine. Fluid, averaging 7.2 l./day, was infused intravenously and an indwelling catheter placed in the bladder to achieve a urinary volume of 4.8 l. every 24 hours. In ordinary cases there was noted a shorter period of unconsciousness, less need of pressure-active substances, absence of hypothermia and renal complications, and less tendency to develop bronchitis.

SODIUM CONTENT OF FISH. Sodium content of raw flesh of both fresh-water and salt-water fish was found to be within acceptable limits for sodium-restricted diets (J. Am. Dietet. A. 36:212, 1960). Average sodium content was found to be 58 mg./100 Gm. in fresh-water fish and less than 20 per cent

greater in salt-water fish. However, salt used in brining or canning may increase sodium content to 400 to 900 mg./100 Gm.

RABIES VACCINE. A new and safer vaccine against rabies is now available, prepared from duck embryos (New England J. Med. 263:1058, 1960). The new vaccine differs from the old Semple vaccine prepared from rabbit brain in being essentially free from the encephalomyelitic or myelin factor. In the more than 5000 patients treated so far with duck embryo vaccine there have been no neurological complications.

CANCER INCREASE IN CITY ANIMALS. Studies on animals in cities as contrasted with rural areas show an increase in cancer in dogs living in urban areas, according to a report to the International Conference on Medical Aspects of Air Pollution. In cats, the increase in carcinoma of the tonsil, esophagus, and stomach may be related to the fact that they lick their fur and perhaps take in the carcinogens in this manner. Scientists in the Soviet Union, Holland, and England have also noted an increase in cancer in animals living in cities.

PROTEOLYTIC ENZYMES. A combination of bovine fibrinolysin and desoxyribonuclease (Elase, Parke-Davis) is reported to be highly effective in enzymatic débridement of necrotic wound tissue and in the liquefaction and dissolution of undesirable exudates of the skin and mucous membranes. The agent is indicated for intravaginal and topical use. It is supplied as a lyophilized powder and as an ointment.

IMMUNIZATION AGAINST INFECTIOUS HEPATITIS. Immunization against infectious hepatitis may be achieved with gamma globulin, according to a report in J.A.M.A. (174:823, 1960). Studies were carried out at a Staten Island children's institution and it was found that gamma globulin was able to suppress the symptoms of hepatitis, mainly jaundice, although it did not prevent infection by the hepatitis virus. After inoculation with gamma globulin, a 30-fold decrease in incidence of hepatitis with jaundice was reported for a five-month period.

VAPOR HUMIDIFIER. Designed to deliver a "fog stream" of moisture-laden air is a compact device weighing 6 lb. The unit can operate for 10 hours without refilling. Water is drawn up from a 2.5 quart reservoir and is micronized within the unit. According to the manufacturer, the vapor does not dampen bedclothes or furniture. The device is marketed as Croupaire by Air-Shields, Hatboro, Pa.

The Eye and the Glance*

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If you want to "collect" *eyes*, you need only enter any museum and look at all the paintings and statuary. But if it is the *glance* you are interested in, nowhere will you find better examples than in Rembrandt's paintings at the Rijksmuseum or in Goya's works at the Museo del Prado.

For both Rembrandt, the magician of light, and Goya, the wizard of shadows, gave up painting the eye and its anatomy to concentrate on the physiological function, seeking not so much to portray the human eye as to capture with their brushes all the splendor of its glance.

For the specialists of today, and particularly for neurologists, the eye is an exquisite coffer filled with subtle diagnostic signs. For ophthalmologists it has become, moreover, a theatre for the most extraordinary surgical operations, in which, as in certain episodes of the Bible, is enacted the sublime miracle of light.

The history of ophthalmology is a unique chapter in the history of medicine because of the superstition, myth, and legend surrounding the eye from the dawn of history. While other sense organs, such as the nose, tongue, or ears, were studied by physicians down the centuries, first empirically and later scientifically, the eye, the most vital of all to man because of the importance of its function and the mystery of its nature, remained a *terra* not only *incognita* but also *mystica*. The eye was not explored for fear of offending the gods, of whose omnipresence the eye itself was a symbol. Hence, the history of ophthalmology is the history of a gigantic conflict between mystic prejudice and practical necessity, a conflict settled only in comparatively recent times by the scientific exploration of the eye. It is also the history of the attitudes of society not only toward the eye but also toward the visual function, reflected in the religions, art, and culture of each period, attitudes so strong that they hampered our knowledge of this organ until the Renaissance, when the "visual" replaced the "auditive" attitude in medicine.

It is enlightening to follow the evolution of the eye in art and its correlation with progress in ophthalmology. In every period in history, the artist's attitude in portraying the eye reflected and often anticipated the medical attitude on this subject Each of these two attitudes, in their turn, sprang from the cultural, religious, and social atmosphere of each period. The human eye was regarded and portrayed as a symbol in mythology, an anatomical part in ancient Greece, an allegory in medieval art, an architectonic part in Renaissance art, an optical instrument in

* An abridged version of this editorial originally appeared in *MD*, the medical newsmagazine, March, 1961.

baroque art, and a functional organ in the Age of Enlightenment. From this last period sprang the streams of thought that led to the current concept of the "cerebral eye," now studied in ophthalmology and depicted in modern art as an organ expressive of the human mind and emotions.

The ophthalmology of prehistoric man was limited probably to the application of clay and vegetable poultices to soothe and protect eyes that had been scratched or injured by claws, thorns, or stones, and to wash away sight-dimming secretions and matter. This crude ocular traumatology was paralleled by the rarity with which the eye was shown in prehistoric paintings, doubtless owing to fear of the magical disasters that might result from portrayal on cave walls of the mysterious organ, which at night winked down by the thousands with a menacing fiery glint from the distant heavens.

A new attitude in art arose in the Mesopotamian, Chaldean, and Egyptian civilizations. The eye then was depicted salient and open, with the lids chiseled to an equal curvature, there being no prolongation of the upper eyelid in Mesopotamian bas reliefs or in the cruel eyes shown in Assyrian art.

In ancient Egypt, except in the time of Akhenaton, the eye was shown naturalistically in sculptures, with a straight edge to the lower lids, the axis between the two corners of the eye stretched horizontally, and the eyes were set close to the nose. In statues the iris was tangential to the upper eyelid, and the glance was fixed and hard, in contrast to its languid and wandering appearance in Egyptian paintings.

The most exemplary portrayal of the eye in ancient Egypt was the Eye of Horus, which made its appearance more than five thousand years ago. According to legend, Horus, son of the goddess Isis, as an infant was attacked and blinded by the demon Set, but recovered his sight when his mother invoked the aid of Thoth, god of learning. Therefore, the Egyptians implored the hawk-headed god Horus to cure their ills, accompanying their pleas with the plucking of lyres made from medicinal woods.

Depicted in Egyptian iconography as an *R* with an eye painted inside the top circle, the eye of Horus became a healing symbol, and *utchats*, or amulets of gold, copper, wood, or wax representing it, were used as protection against ocular infections and sore eyes. Later, Horus was supplanted by other gods, since fashion has ruled even in the popularity of gods. In the Middle Ages the Eye of Horus reappeared in the form of a sign similar to the figure 4, which physicians and alchemists wrote on their prescriptions to invoke divine aid, thus resuscitating the Roman custom of writing the sign of Jupiter for similar purposes.

The R_x sign was introduced by the physician Krinas in the time of Nero as a graphic symbol that the physician—and Christianity—was subject to the power of the state. In the Middle Ages, in a typical swing of history's pendulum, the Church, in its struggle against medieval paganism in countries like Spain, compelled physicians to use the initials of the *Responsum Raphaelis* instead of the heathen sign for Jupiter. Thus, little by little, the sign of Horus became confused with that of Jupiter and turned into the R_x, which is still used today in the upper left-hand corner of prescriptions.

Egypt's glaring sun and the sandstorms that forever fill its air with a floating infinity of silica and mica grains—tiny mirrors that give the Egyptian air that magic luminescence—were among the factors responsible for the large number of eye diseases in that country. Exposure to the glaring sun, heat, wind, and dust provoked a hyperemia of the bulbar conjunctiva, and, just as the skin reacts to such a climate by turning freckled or tanned, the eye developed a delicate web of dilated blood vessels that made it more susceptible to morbid processes.

The frequency, in ancient times just as now, of trachoma and other eye conditions in Egypt spurred specialization in ophthalmology. Again, to prevent the ocular deformation that occurs at death, the Egyptians filled the eye sockets of the dead with linen compresses on which was painted the iris, and then covered the whole thing with the eyelids, or they filled the sockets—as in the mummy of Ramses I—with tiny onions, whose magic properties were of additional value.

This intimate association of the eye with religious symbolism hampered the scientific study of the sight organ for thousands of years. However, people living in areas of the globe—such as the Middle East, cradle of civilization—exposed to furious and unending sandstorms, which brought on ocular irritations often followed by infections, were compelled to seek some remedy against the atrocious penalty of blindness. This is why in ancient Egypt servile submission to the dogmatism of magic medicine contrasted sharply with the empirical development and study of medications for curing eye affections.

Even so, the frequent mention of blind people in the songs and legends of ancient Egypt bears witness to the appalling prevalence of blindness among Oriental peoples. Often these blind beggars became immortal bards, as if their loss of the precious gift of being able to contemplate the wondrous world around them was compensated by the power to contemplate and sing of the wondrous world within them—a world in which was reflected, as in a magic mirror, the vast tapestry of the outside world as seen through eyes deprived of light but filled with a sublime poesy.

The ancient civilizations came and went. Centuries passed. Until one day, some 2500 years ago, in sun-drenched Greece and its adjacent islands, a handful of men, philosopher-physicians, posed transcendental questions on man and nature that would thereafter guide mankind on the path to civilization and establish the dignity of man. In art a noble type of statuary developed, which portrayed the Greek gods like men and the men like gods. Intended for a people that liked to keep moving all the time, Greek art concentrated on sculpture, a dynamic three-dimensional art form that requires the spectator to walk around it to better appreciate it. In contrast, medieval art was primarily two-dimensional and static, intended for crowds that stood still and agape in front of a stained glass window, an altar screen, an icon, or a mural fresco.

It was the custom of Greek sculptors to leave out the pupil and trace only the eyelids, suggesting the glance only by the shading of the eyelids. Sometimes, in busts of emperors, they indicated the transparency of the cornea by making a hole in place of the iris and filling it with solid material to reflect the light. Greek artists depicted the eye as an anatomical part but only as seen from the outside, its internal structure being to them somewhat of a mystery. The wise Aristotle,

however, although like the Greek artists he too did not correlate the eye with the human body, already denied that the vision was produced by rays emanating from the eye and impinging on the objects seen. The Stagirite, however, studied only the eyes of animals, mainly fish. When the Greek Ptolemies authorized vivisection at the School of Alexandria—to the horror of the Egyptians, who reveled in zoolatry, worshipping cats, sacred bulls, scarabs, and crocodiles in their mighty temples—the eye was finally dissected and described as much as it was possible without the aid of a microscope, and its parts were given names still used today. The retina, for instance, was compared by Herophilus to a net, because of its resemblance to the fishing nets used by the Greeks. It was then that the error—perpetuated for centuries by Galen—originated to the effect that the optic nerves were hollow and that vision was due to fine rays, like gossamer threads or delicate tentacles, which made an object visible on contact. This concept of the eye as a mere anatomical organ caused optical progress to be confined solely to catoptrics or the study of reflection, and little attention was paid to dioptrics or the refraction of light through transparent bodies.

As a symbol of strength and luminosity, clarity and power, the eye embodied divinity in Greek mythology. Plato used to say that we "look" with concepts; and he also stated that an idea is a "point of perspective." In mythological iconography, according to Cirlot, the magic powers of the eye were stressed by means of three processes: *displacement*, or placing the eyes in other than anatomically normal positions (heterotopic eyes in the mythological images of Pan or on the wings of Romanesque angels); *diminution*, or reducing the number of eyes (the one-eyed Polyphemus and Cyclops); and *augmentation*, or increasing the number of eyes (the hundred-eyed Argus of Greek mythology).

To these processes should be added the conversion of the eye into a protective magic talisman, such as the eyes painted on Greek galleys and, later, the Oriental eye amulets and eyes painted on the faïence orbs used by Indochinese religious sects.

Cirlot also drew a contrast in the three attitudes adopted by man upon facing the Infinite to inquire about his fate: the symbol of the *wall*, representing a feeling of impotency before the Infinite, for instance, the Wailing Wall of the Hebrews in Jerusalem; the symbol of the *window*, representing a feeling of possible but restricted human activity, for instance, the perforated jade disks of the Chinese; and the symbol of the eye talismans, which is not an impossibility like the first symbol, nor an opening offering escape, like the second, but an answering *mirror* in which man, looking into it as into his own eye, can find within himself the answer to his anguished query.

Ceasing to be an anatomical representation, the eye became allegorical in Byzantine paintings, which depict the basileis with expressionless eyes that look only straight forward or sideways, while in the ancient Christian Gnostic images the eye became a symbol of God, and in Arabic and Persian paintings it became an allegory of the wisdom or power of caliphs, viziers, and physicians. Under the compulsion of the ocular scourges inflicted by their deserts, the Arabs, victims of "Egyptian ophthalmia," or trachoma, and of other sight afflictions, excelled in practical ophthalmology. Although their religion forbade dissection of the eye, they made progress

in its clinical and surgical treatment. *The Arabian Nights*, whose tales bear witness to the great medical wisdom of the Arabs in the ninth century, abound in blind characters, sometimes kindly and unfortunate, sometimes crafty and cruel, who file through its pages like a tragic chorus.

The Arabs left us several masterly treatises in ophthalmology, the oldest drawing of the human eye, and the magnificent work on optics by Alhazen, who anticipated Leonardo da Vinci and Giambattista della Porta in comparing the eye to the camera obscura.

In that very visual world of allegory of the Middle Ages, artists were interested more in the eye as an allegory—of God, as well as of the powers of darkness in the allegories of Satanism—than as an anatomical organ, and they presented a slightly protuberant eye, immersed in concentration, meditation, and mystery. Thus Giotto, to express mental concentration and somber sorrow, lengthened the lid to form a triangle. In their turn, the Virgins and Saints of Botticelli, Fra Filippo Lippi, Ghirlandajo, and Il Perugino had eyes set wide apart, very symmetrical and straight, with only the edge of the upper eyelid curved and with a diagonal crease from the inner corner to the cheekbone, which lent the face serenity, just as the long arch of the brows gave it an air of naiveté.

Art was no longer collective in the late Middle Ages, when, as the glance became of greater interest than the eye itself, optics advanced more than did clinical ophthalmology, though, of course, advice was given on ocular hygiene. The *Regimen Sanitatis Salernitanum* contained a recommendation to wash the hands after meals, since "Tis wholesome, cleanely, and relieves your eyes."* This was possibly a survival from the Talmudic tradition, since on taking salt after a meal it was customary to avoid contact between the hands and the eyes during the postprandial prayer.

In spite of the prevailing ignorance about the eye, a visual hunger eventually led to the discovery of reading glasses and the beginning of the optical industry.

The theoretical science of perspective in turn was born, according to Sarton, with Filippo Brunelleschi, who invented the first optical instrument after the invention of spectacles. His instrument, called a *perspicillum* (perspective glass or telescope), was a wooden tablet on which was painted a fine colored miniature of the Cathedral Square in Florence as seen from a point three feet inside the main door of the cathedral. He covered the sky in the picture with a polished silver plate, so that the real air and sky of Florence were reflected with the moving clouds on the silver plate. In the front of the painting, where the line of sight met the painted scene, Brunelleschi bored a hole, the size of the pupil of the eye, going right through the wood. Then, by placing a mirror at arm's length opposite the painted tablet, if one looked through the hole from behind the tablet at its reflection in the mirror, the picture was seen exactly from its right point of perspective and seemed to be "the proper truth and not an image." Centuries later this apparatus was reversed to allow the light to enter through the hole and project the outside

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* Lotio post mensam, tibi confert munera bina
Mundificat palmas et lumina reddit acuta
Si fore vis sanus, ablue saepe manus.

scene on a waxed screen in the camera obscura, but credit is due to Brunelleschi for having paved the way to this important discovery.

The passionate interest during the Renaissance in architecture, not only of buildings but also of the human body, considered as a *fabrica* by Vesalius, was reflected in the architectonic conception of the eye. In the pictures of the period the eye already appeared endowed with a glance, but the artist was still more concerned with its outer structure, just as Vesalius was more interested in building up a "fabrica" than in setting it in motion. The eye as painted by the Renaissance artists remained static, but it was architectonic and correlated with the rest of the face.

With Leonardo da Vinci a new visual attitude in art and science commenced, the *saper vedere* that laid bare the mysteries of the human eye, its anatomy, its physiology, and, above all, that led to the correlation of form and function, or the eye and the glance.

For Leonardo the eye was "the window of the soul"—as he described it in his *Codex Atlanticus*—which was why he studied, dissected, and sketched it with so much care. Leonardo—whose anatomy was still Galenic, just as his physiology was Aristotelian—did not give the crystalline its correct position in the eye, a point on which even Vesalius was mistaken. This was not done until the time of Felix Platter. The reason for such error was that Leonardo studied only the eyes of myopic bulls, fixing them in whites of egg and coagulating them by boiling. While he was sectioning the crystalline lens, whose hardness made cutting difficult, it probably moved so that Leonardo never found it in its right place. Nor was Leonardo able to explain how the human brain created an upright image from the inverted visual image.

Leonardo's knowledge of optics and his *saper vedere* were applied to the marvelous portrait of the gelatinous-like Mona Lisa, whom Leonardo painted in two halves: the right half Madonna-like, contemplative, serene, judicious; the other half smiling but sly. To obtain that effect he made the eyelids more elongated and ovoid on the smiling side than on the placid side of the face, leaving it to the onlooker to effect in his mind the synthesis of the portrait, in whose smile flutters an inner world of mysterious magic and bewitching charm.

It was especially in the Baroque Age that the glance was granted full artistic recognition in the paintings of El Greco, Velázquez, Zurbarán, and Rembrandt, who made of the eye a magician that gave light and expression to the face. This tendency to appreciate the glance more than the eye found a parallel in the attitude of physicians. William Harvey, the outstanding investigator of the baroque, was called "the ocular philosopher" by Sir Thomas Browne. This attitude, inspired by Leonardo's *saper vedere*, that is, the desire to see the world and its peoples not symbolically or allegorically but as they really are, led, through interest in studying the visual function, to a better knowledge of the eye. Leonardo and the painters of the Renaissance and the Baroque thus awakened a fresh interest in the act of seeing, in knowing how to look at things, turning sight into the most valuable instrument for exploring the world.

The romantic yearning of the Age of Enlightenment stimulated investigation of the mysteries of the visual infinity of the human eye. We have mentioned elsewhere

that while Vermeer in Delft was painting the minutest details of Dutch interiors in his exquisite miniatures, only a few blocks away Leeuwenhoek, in a similar desire to examine the minute, was studying the crystalline and retina in his homemade lenses.

The greatest figure in the Enlightenment, the prodigious Goethe—who said in his *Poetry and Truth* that "Medicine occupies the whole man because it is concerned with man as a whole"—studied light and color all his life. In his hour of death his last words were symbolically a demand for "Light! More light!" This "ocular" psychology of Goethe explains why his memoirs, novels, and visions so abundantly used visual imagery. To put himself to sleep, Goethe would "see" in his mind a seed gradually growing into a plant. His admiration for the eye was expressed in his phrase, "... *gegen das Auge ist das Ohr ein stummer Sinn.*" ("Compared with the eye, the ear is a mute faculty.")

Goethe based the science of chromatics on the study of turbidity, color being his favorite subject of study, ranging from observation of the phenomenon that if, after admiring a red rose on a bright, sunny day, immediately afterward one shifts the eyes to a white background, the image of the rose is reproduced in green, to the analysis of the secret of the colors of the autumn moon, which takes on orange and crimson tints when seen through a mist. With Goethe, investigation into the function of the ocular organ considered as an optical instrument reached its peak. It is symbolical that this global and "encyclopedic" perspective of ophthalmology was developed at the same time as Diderot and the other Encyclopedists were introducing "encyclopedic" concepts in politics.

Such was the road followed by the present wondrous science of modern optics—from the initial naturalistic external observations to Brunelleschi's artistic device, to the work of della Porta, Leonardo, Galileo and his lenses, Leeuwenhoek, and Goethe and his theory of colors, to our great modern achievements.

Modern ophthalmology can claim a whole arsenal of triumphs: internal repair and dissection of the eye; analysis of its function; interpretation of ocular signs; anti-infectious ocular chemotherapy, of great value in saving human eyesight; biochemical ocular research; the remarkable developments in modern ocular surgery; intracapsular cataract extraction; diathermocoagulation for retinal detachment; corneal grafts; contact lenses; and the conquest of ophthalmia neonatorum. All these victories have made ophthalmology one of the cleanest and most perfect specialties, in which, though physical instrumentation is a vital factor, still more important are the hands and brain of the man handling the instruments.

It would be interesting, first, to analyze the correlation between art and ophthalmology in modern times; second, to study the parallelism between the impressionists' attempt to capture light in their pictures, sometimes splitting it up into tiny luminous dots (as in Seurat's pointillism), and the coinciding interest of ophthalmologists in the vision of light and color; and third, to analyze the resemblance between the surrealist attitudes of Ernst, Magritte, and Dali—who have used the eye so much as a powerful magic symbol (returning thus to the original eye symbolism of mythology) and as an organ expressive of human thought and emotion, that is to say, of what goes on in the brain—and the modern concept of a cyclopean "cerebral

eye" formed by the visual centers and their correlation to the eyes. This concept had already been anticipated by Descartes when he tried to chase the elusive butterfly of the relationship between body and mind.

We began by speaking of the "glances" in Goya's paintings. Goya was a painter of glances. His secret, as analyzed by a Spanish oculist, consisted in painting the iris two millimeters larger than life, thus increasing the expression in the glance by contrasting the enormous iris with the white background of the sclerotic against which the iris stands out. Be that as it may, in the same way that art has proceeded successively from portrayal of the eye as a "bulge," to portrayal of its light, and finally to portrayal of the "idea" and the feeling expressed by the eye, so also has scientific study of the eye progressed from physical observation to ocular optics to the psychoneurological study of the "cerebral eye."

Ophthalmological study of the eye is now focused on its glance—function—rather than on its anatomy. This triumph of the glance is exemplified in the progress made with contact lenses, which besides correcting vision can alter the appearance of the glance, a valuable thing in photography, television, movies, and art. To the artist—even to an iconoclast like Picasso, who has disintegrated and displaced the ocular organ (and every iconoclast is a believer at heart, since if he did not believe in the religious merit of saintly things he would not try to destroy them)—the eye is a tiny cathedral of the human being, a cathedral through whose stained glass windows—the pupils of the eye—the light of God enters into man, and the light of man's soul shines out on the world.

Group to Study Tuberculosis Facilities

The U. S. Public Health Service has announced appointment of a committee to study changing hospital needs of tuberculous patients that have resulted from improved methods of treatment and consequent shorter periods of hospitalization. Organized in cooperation with the American Hospital Association and the National Tuberculosis Association, the committee will analyze data on the incidence of tuberculosis and the use of tuberculosis beds, to determine the future needs for tuberculosis facilities, and will draw up suggestions to guide communities in construction of new facilities and conversion of existing facilities for other uses.

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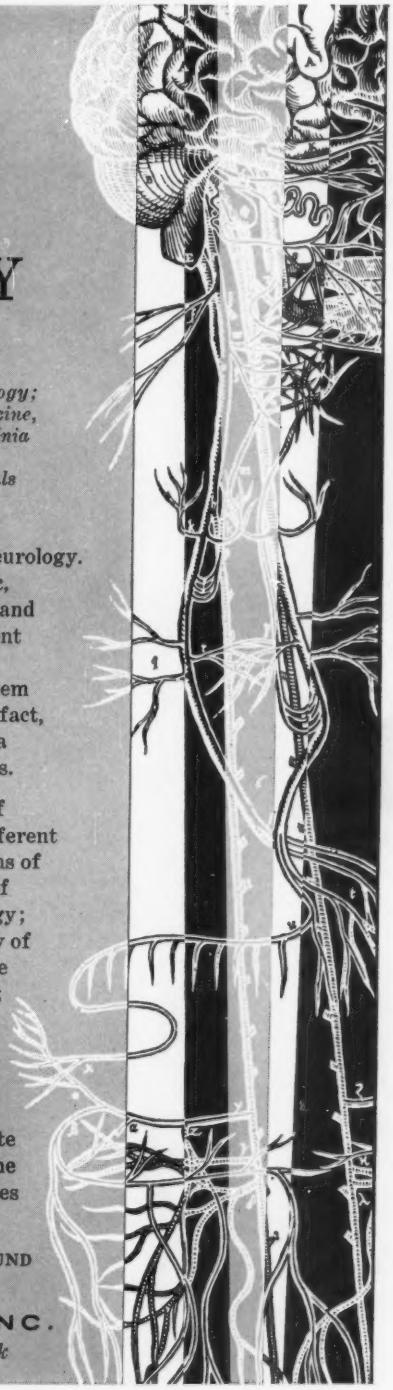

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A New MD Medical History...

A HISTORY *of* OPHTHALMOLOGY

by George E. Arrington, Jr., M.D.

Associate in Ophthalmology, Medical College of Virginia, Richmond, Virginia

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